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GLYCOGEN STORAGE DISEASE OF THE HEART

CLINICAL OBSERVATIONS IN FIVE INFANTS

SIDNEY FRIEDMAN, M.D., AND RACHEL ASH, M.D.
PHILADELPHIA, PA.

BECAUSE glycogen storage disease of the heart is a rare disease, the clinical data accumulated from five infants in whom this diagnosis was confirmed at autopsy seems worthy of presentation. In recent reports,[1, 2, 3] the similarity in clinical manifestations among infants with glycogen storage disease of the heart and amyotonia congenita has been stressed. It is our purpose to emphasize this aspect of the clinical picture since the generalized skeletal muscle involvement rather than the cardiac manifestations dominated the clinical course of our five patients.

The rarity of glycogen storage disease of the heart is well documented. In 1950, di Sant Agnese, Andersen, Mason, and Bauman[4] accepted only fourteen cases from the world literature, acknowledging the probable existence of others in which the diagnosis was not conclusively proved. In 1954, Rossi[5] estimated that less than forty cases had been reported to that date. The familial nature of glycogen storage disease of the heart is recognized.[6] A recessive and perhaps sex-linked mechanism of transmission has been suggested.[7] The involvement of multiple siblings in a single family has been reported.[8, 9] Consanguinity has been a finding in several families.

The existence of two main varieties of glycogen storage disease has been described on clinical grounds for many years; namely, the hepatic form originally described by von Gierke in which the liver and kidney are the primary sites of glycogen deposition, and the nonhepatic or cardiac form in which the myocardium and skeletal muscles are primarily involved. The studies of Cori[10] have demonstrated a chemical difference between these two entities. Von Gierke's disease, or glycogen storage disease of the liver, is marked by hepatomegaly, renal enlargement, and retarded somatic growth. Hypoglycemia, ketosis, and hyperlipemia can usually be demonstrated together with a diminished response to epinephrine administration. Cori has shown that the glycogen structure in these patients is essentially normal, but that a definite decrease in the amount of the enzyme, glucose-6-phosphatase, is present. This enzyme is

From the Department of Cardiology of the Children's Hospital of Philadelphia and the Department of Pediatrics, School of Medicine, University of Pennsylvania.

responsible for splitting off phosphate from the glucose molecule and thus permitting its passage into the circulation and delivery to the tissues. A deficiency of this enzyme would likewise impair glycogenolysis. The chief product of glycogen breakdown is glucose-1-phosphate which is then converted to glucose-6-phosphate. Impaired breakdown of the latter component, due to the enzyme deficiency, leads to its accumulation and slowing of the reversible reactions leading from glycogen to glucose.

In contrast to von Gierke's disease, glycogen storage disease of the heart and skeletal muscles is not associated primarily with hepatomegaly and evidence of impaired carbohydrate metabolism. In this disease, muscle weakness, cardiac enlargement, and enlargement of the tongue have been prominent findings. Structurally normal glycogen is found in the involved organs and the amount of glucose-6-phosphatase is apparently normal. At present, no satisfactory chemical explanation is available for the precise metabolic abnormality present in this type of glycogen storage disease. Cori[10] and Recant[11] have listed two other very rare and unusual clinical varieties of glycogen storage disease in which deficiencies in the enzymes responsible for synthesis or breakdown of the branched structure of the glycogen molecule have been demonstrated. The glycogen in the tissues of affected individuals has been found to be of abnormal structure.

Two clinical reports have recently described patients with a nonhepatic form of glycogen storage disease in which the skeletal muscles have been primarily involved with relatively little deposition of glycogen in the myocardium. In the two patients reported by Krivit and associates[2] profound muscle weakness was present, suggesting initially the diagnosis of amyotonia congenita. A primary muscular dystrophy with deposition of glycogen in skeletal muscle was finally diagnosed in each case; no neurological disease was demonstrable. The deposition of small amounts of glycogen was described in the cardiac specimen in one of these cases and increased cardiac weight was found at autopsy in the other. However, both of the patients demonstrated normal electrocardiographic tracings and normal cardiac silhouettes in roentgenograms taken during life. Similarly, the first case described by Zellweger and co-workers[3] also showed extensive skeletal muscle infiltration with glycogen, but a normal heart size was demonstrated on roentgenographic examinations and a normal electrocardiogram was recorded. It thus appears that the relative degree of skeletal or myocardial involvement can vary over a wide range in the nonhepatic form of glycogen storage disease. Patients may demonstrate primarily skeletal or primarily myocardial involvement, or mixed degrees of involvement. In each of the five patients included in the present study, extensive skeletal as well as cardiac muscle involvement was noted both clinically and pathologically. This combined form of involvement in nonhepatic glycogen storage disease is apparently more common than the primary skeletal muscle variety.

The duration of life in most patients with glycogen storage disease of the heart has varied from a few hours to nine months. In the review of Landing and Bangle,[7] several earlier cases,[12]

which were reported to have survived for longer periods of time, were considered by the authors to represent another disease entity. Most patients with this disease have eventually succumbed to the complications of respiratory muscle weakness, presumably caused by the deposition of glycogen in these muscles. Relatively few have been reported to have died in a state of congestive failure. No form of treatment has altered the uniformly fatal outcome.

CLINICAL OBSERVATIONS

Since the clinical and pathologic findings in the five infants included in this report are very similar, the details of only a single case will be reported fully. Pertinent clinical findings in all of the five cases have been summarized in Table I. A typical electrocardiographic tracing is presented in Fig. 1. Representative roentgenograms of the chest are presented in Figs. 2 and 3.

CASE REPORT

L. G., a negro male infant, died at the age of 4½ months, one month following admission to the Children's Hospital of Philadelphia. The chief complaint on admission was cough associated with fever of three days' duration.

Family History.—The immediate family consisted of two healthy parents and an 8-year-old half sister born of the mother's previous marriage. The half sister was reported to have congenital heart disease for which she was operated upon elsewhere. At present she also demonstrates evidence of rheumatic heart disease. The patient was the product of the first pregnancy of his parents; a subsequent male offspring is now living and well at the age of 11 months.

The mother had six siblings, all of whom were living and well except one who suffered an accidental death. The father had ten siblings of whom two died in infancy; the first of these succumbing to pneumonia prior to the father's birth. When the father was 13 years old, another younger sibling was born who demonstrated listlessness and weakness associated with a paucity of spontaneous movements. This infant died suddenly during the course of a feeding at home and aspiration pneumonia was suspected. No hospitalization or post-mortem examination was carried out on either of the father's deceased infant siblings.

History of Present Illness.—The patient was born following a 9-month, apparently normal pregnancy with a birth weight of 3,295 grams. No neonatal difficulties were noted. The infant was breast fed for two months and thereafter fed an evaporated milk formula. Supplementary vitamins were administered from birth.

The infant visited the Well-Baby Clinic of the maternity hospital at 1 and 2 months of age. A hernia and hydrocele were detected and plans were made for their future repair. Approximately three days prior to admission a fever associated with cough was noted. Listlessness was also apparent for the first time during this interval. Feedings were taken poorly and some regurgitation occurred. Excessive mucus in the nasopharynx was also noted. A tentative diagnosis of pneumonia was made at the time of admission.

Physical Examination.—Examination on admission revealed a well-nourished and hydrated Negro male infant with mild respiratory distress and a fairly strong cry. Mild retractions of the chest wall were noted with each inspiration. No cyanosis or jaundice was evident. The pulse rate was 136 per minute; respiratory rate 36 per minute; temperature 101.2° F. The body weight was 5,305 grams; the head circumference, 16 inches;

TABLE I. SUMMARY OF CLINICAL FINDINGS IN FIVE INFANTS WITH GLYCOGEN STORAGE DISEASE OF THE HEART AND SKELETAL MUSCLES

CASE NO.	SEX/ COLOR	AGE AT ONSET OF SYMPTOMS	AGE AT HOSPITAL ADMISSION (MO.)	AGE AT DEATH (MO.)	MATERNAL AGE	PATERNAL AGE	BIRTH ORDER	BIRTH WEIGHT (GM.)	FAMILY HISTORY	CHIEF COMPLAINT	CARDIAC MURMUR	CARDIAC ENLARGEMENT
1.	W/M	3 wk.	2	5½	25	28	2nd	3,060	–	Cough, hoarseness, weakery, poor wgt. gain	+	Moderate
2.	C/M	3 mo.	3½	4½	29	33	1st	3,295	+	Cough, fever	+	Moderate
3.	C/F	Birth	5	7	28	36	4th	1,515	–	Poor development, cough, rapid breathing	+	Moderate
4.	C/F	3 mo.	7	8½	30	50	8th	----	+	Fever, cough, noisy respirations	–	Slight
5.	C/M	2 mo.	3½	5	24	45	5th	3,970	+	Recurrent upper respiratory tract infections	+	Moderate

chest circumference, 15 inches; and body length, 26 inches. Secretions were present in large amounts in the nasopharynx. Over both lung fields coarse breath sounds but no fine râles could be heard. Cardiac enlargement to the left was suspected on percussion. A low-pitched, soft systolic murmur was audible to the left of the mid-sternum; no murmurs were audible posteriorly. No thrills or diastolic murmurs were detected. The liver edge was palpable 2 cm. below the right costal margin. A left hydrocele and left inguinal hernia were present. No obvious neurological manifestations were evident at this time; all reflexes were present and normal.

The diagnostic impression at the time of admission was upper respiratory tract infection, possibly associated with pneumonitis. A roentgenogram of the chest taken at the time of admission showed cardiac enlargement but no evidence of pneumonia or of increased pulmonary vascular markings.

Laboratory Studies.—Hemoglobin level on admission was 9.2 Gm. per cent; little variation occurred during the one-month period of hospitalization. The white cell count on entry was 8,000 and reached a peak of 13,000 approximately one week prior to death. The differential white blood cell count varied, at times showing a predominance of lymphocytes and, on other occasions, a majority of neutrophils. Urinalysis revealed a specific gravity of 1.017 and a pH of 5; no excessive amounts of protein, sugar, or acetone were detected; microscopic examination was negative. A sickling preparation was negative; an old tuberculin skin test in a dilution of 1:1000 was also negative. A blood culture on admission was sterile; cultures of the nasopharynx on multiple occasions revealed no unusual organisms. An electrocardiogram, taken on the day following admission, revealed very high amplitude QRS complexes in all leads with depression of the S-T segments and negative T waves in the limb leads. Roentgenographic examination of the chest was repeated on two occasions and demonstrated no change in the degree of cardiac enlargement. Approximately one week prior to death, atelectasis of the left lower lobe was evident on roentgenographic study.

Blood chemistry studies were as follows: NPN, 36 mg. per cent; cephalin flocculation, negative; thymol turbidity, 1.4 units; serum protein, 5.5 Gm. per cent; serum albumin, 2.4 Gm. per cent; serum globulin, 2.1 Gm. per cent; cholesterol esters, 121 mg. per cent. The serum mucopolysaccharides were found to be normal in total amount and in their electrophoretic pattern. The red blood cell glycogen content was found to be normal, i.e., equivalent to controls. A fasting blood sugar was 79 mg. per cent and one hour after epinephrine was given the blood sugar level rose to 173 mg. per cent. The fasting serum pyruvate was 1.24 mg. per cent, and twenty minutes after the injection of epinephrine the pyruvate level was 2.92 mg. per cent; one hour later it was 2.33 mg. per cent. The response of the blood sugar and pyruvate levels to epinephrine administration was considered normal. The serum levels of sodium, potassium, chloride, and CO_2 were within normal limits.

Hospital Course.—The patient was promptly started on antibiotic therapy but the fever failed to subside. On the fourth hospital day, marked muscular flaccidity and lethargy were noted. Because of this finding associated with cardiac enlargement, a biopsy of the left gastrocnemius muscle was performed. The specimen of muscle showed focal areas in which marked vacuolization of the cytoplasm of the muscle fibers was present. Progressively increasing muscle weakness and flaccidity developed until the infant was unable to suck or swallow; gavage feedings were necessary. Because of some increase in liver size and the presence of respiratory distress, digitalization was attempted.

Gross arrhythmia resulting from digitalis intoxication appeared shortly after one half of the calculated amount of digitalis was administered. This disappeared with a reduction in the dose of digitalis. The difficulties arising from large amounts of tenacious mucoid material in the nasopharynx became progressively greater. Frequent aspirations of the nasopharynx were inadequate and finally a tracheotomy was performed. Death occurred at the age of 4½ months, one month after admission.

Post-mortem examination was carried out promptly. Almost the entire heart, 60 grams of liver, and 20 grams of psoas muscle were frozen within one hour of death. Portions of these tissues were sent in the frozen state to the laboratory of Dr. G. Cori where the following chemical analyses, shown in Table II, were made.

TABLE II

TISSUE	% GLYCOGEN	% GLYCOGEN END-GROUP	% GLYCOGEN SPLIT BY PHOSPHORYLASE	AMYLO 1-6-GLUCOSIDASE IN UNITS/100 MG.
Heart	6.6	6.9	47	120
Psoas	13.0	7.1	42	131
Liver	6.2	7.9	39	—

It was concluded that these tissues contained glycogen of normal structure as well as a normal amount of amylo 1-6-glucosidase, the enzyme responsible for splitting the 1-6-glucosidase linkages which produce the branched structure of the glycogen molecule.

Necropsy Findings.—The heart weighed 46 grams. The systemic and pulmonary venous return was normal as were the great vessels, valves, and septa. The papillary muscles of the left ventricle presented a diffuse gray-pink color which was evident through the transparent endocardium. The left ventricle was hypertrophied and somewhat dilated. Microscopically, the myocardial fibers were increased in size and showed prominent irregular hyperchromic nuclei. The cytoplasm was almost entirely displaced by large vacuoles which stained positively with Best's muciearmine and periodic acid-Schiff stain.

The liver was enlarged; its surface was smooth and glistening; the edge was sharp. On section, the color of the liver was pale yellow and the architecture appeared normal. Microscopic examination of the liver revealed marked vacuolization; the cell nuclei were in an eccentric position. Special staining techniques demonstrated that the vacuoles contained material with the staining characteristics of glycogen. Skeletal muscle fibers also showed marked vacuolization and apparent loss of cytoplasm. Both lungs were purplish-red and fleshy. There were scattered areas of hemorrhage present. On section there were small collapsed areas and areas of crepitation. Congestion and edema were marked. The trachea and bronchi were filled with a greenish exudate. Microscopic examination of the lungs showed focal areas of atelectasis. Many alveoli were filled with proteinaceous material. The tracheobronchial lymph nodes were enlarged.

DISCUSSION

A review of the family history in each of the five infants studied provides further information to support the genetic determination of glycogen storage disease of the heart. Two of our five patients were born to the same parents; a third male offspring in this family also died in early infancy and, although a post-mortem examination was not performed, showed an abnormal electrocardiogram

compatible with the presence of glycogen storage disease of the heart. Thus, in a single family, there were probably three cases of glycogen storage disease, two females and one male, in addition to four older siblings who are living and well. Since the diagnosis in one male and one female infant was confirmed at autopsy, the conventional form of sex-linkage in the genetic transmission of this disease seems unlikely. In another instance, both an older half sibling of the same mother, and a younger subsequent sibling of the same parents are known to be free of glycogen storage disease of the heart. A review of the family history in this case revealed two neonatal deaths among siblings of the father. No definite history of consanguinity could be elicited in any of the families.

The obstetrical history in each of our five cases was not unusual. The birth weight of each of the five infants was above 3,000 grams except in the case of one premature infant who was one of twins, the sibling dying at the time of birth. The birth order of the involved infant within each family varied from the first to the eighth position. Three of the infants were males and two were females; four were Negroes and one white. Maternal age ranged from 25 to 30 years; paternal age from 28 to 50 years.

The average age of the patients on admission to the hospital was 4 months with a range of 2 to 7 months. Symptoms were first recognized at least one month prior to admission in four of the five cases and in two instances dated from the neonatal period. From the sequence of clinical events in these five patients, the onset of definite symptoms may be expected by the age of 4 to 6 months. The absence of symptoms at the age of 6 months would be strong evidence of the absence of this disease. The average age at the time of death was 6 months with a range of 4½ to 8½ months. No single factor seemed to be related to longer survival.

The hospital course in each instance was progressively downhill with occasional temporary plateaus associated with the successful treatment of secondary bacterial infections. Death in all instances resulted from aspiration, pulmonary infection, and pulmonary complications. In no instance was frank congestive heart failure observed. Because of the presence of respiratory distress and known cardiomegaly, digitalis was employed in two cases without apparent benefit. In both instances, digitalis intoxication was induced, suggesting the possibility that the myocardium in these infants was particularly sensitive to the effects of digitalis. The amount of digitalis administered prior to the appearance of toxic symptoms was relatively small in both instances.

The most striking physical findings noted in these five patients were those pertaining to the neuromuscular system. Paucity of spontaneous movements, generalized muscle weakness, and diminished deep tendon reflex responses were consistently present and progressive in all patients. Despite the obvious muscle weakness, palpation of the involved skeletal muscles in several instances revealed them to be of average or slightly greater than average size with a firm, rubbery consistency suggestive of muscles observed in pseudohypertrophic muscular dystrophy. Respiratory distress was also

readily apparent as the result of the accumulation of secretions in the respiratory tract.

Attention was usually directed to the heart by the demonstration of cardiac enlargement either on physical examination or in routine roentgen examination of the chest. A cardiac murmur was detected in four of the five patients. These murmurs were of low intensity and low pitch, best heard to the left of the lower sternum or over the mid-precordium and would not ordinarily be considered significant murmurs. There were no associated thrills or diastolic murmurs. In only one of the five infants was a murmur audible over the posterior chest wall. Gross enlargement of the liver was never observed although the liver edge was palpable below the level of the right costal margin in four of five cases. The spleen was not palpable in any of our patients.

Approximately a dozen electrocardiographic tracings recorded from patients with glycogen storage disease of the heart have been reported in the medical literature to date; only about half of these have been reproduced and are available for review. In 1954, Johnson[13] outlined the electrocardiographic alterations observed in this condition in five tracings then available. He noted certain similarities among these tracings and listed the following characteristic features: (1) tall, upright QRS complexes in Leads I and II, inverted in Lead III; (2) depressed S-T segments in all standard leads; (3) inverted T waves in all standard leads; (4) elevated S-T segments in the right-sided precordial leads and depressed S-T segments in the left-sided precordial leads; (5) upright T waves in the right-sided precordial leads and inverted T waves in the left-sided precordial leads. Rossi[5] recently reported his observations on five additional tracings recorded from seven of his own patients with glycogen storage disease of the heart. A sinus tachycardia was present in all; high as well as low voltage complexes were observed, and right-sided as well as left-sided tracings were found to be compatible with this diagnosis. The consistent depression of S-T segments and the finding of negative T waves in the standard leads as well as in the left-sided precordial leads were also observed by Rossi.

Electrocardiographic tracings were available in four of the five infants described in this report, including precordial leads in three cases. A typical tracing is shown in Fig. 1. In general, the findings were similar to those previously reported. All tracings showed a sinus tachycardia or normal sinus rhythm. The QRS complexes were of very high amplitude in all of the four tracings; the average height of the R wave in standard Lead I was 28 mm. The P-R interval in the four tracings varied from 0.08 to 0.10 second; none were prolonged to the upper limit of normal. The Q-T interval varied from 0.27 to 0.29 second, also within the range of normal.

In Lead I the P waves were found to be notched in two tracings and to be peaked in Lead II in all four. The amplitude of P_2 was greater than 2.5 mm. in only one patient. The QRS complexes in the standard leads showed no axis deviation in any of the cases. The Q waves were of progressively increasing depth from Lead

I to Lead III. There was a prominent R wave over the right side of the chest in the three instances in which precordial leads were available. Over the left side of the chest the QRS complexes were diphasic with the R wave somewhat larger than the S wave. In Lead aV_R, a prominent S wave was present in two cases and a diphasic QRS was present in one instance.

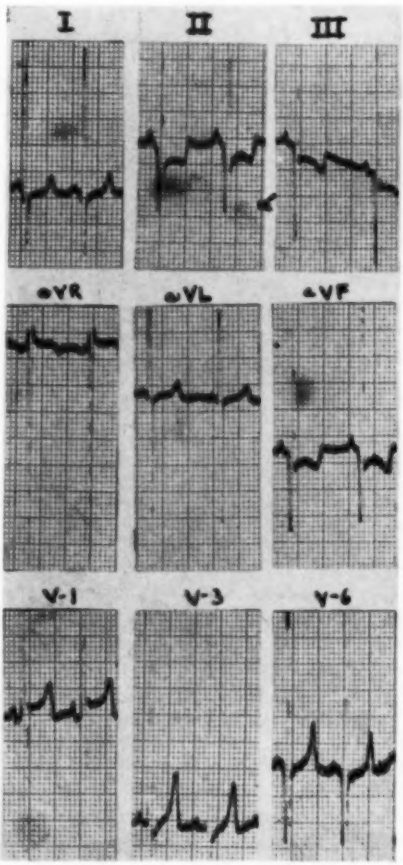

Fig. 1.—Electrocardiogram recorded from 2-month-old infant who died three and one-half months later of glycogen storage disease of the heart and skeletal muscle system. Tracing demonstrates high amplitude QRS complexes, marked S-T and T-wave changes, and prominent Q waves in the limb leads; evidence of biventricular enlargement in the precordial leads.

Depressed S-T segments were found in the limb leads in three of our four cases. This depression was of a severe degree, involving Leads II and III most commonly; Lead I also showed this abnormality in two cases. Negative T waves were present in all three standard limb leads in three of the four cases; in the remaining case, only in Leads II and III. Late inversion of T and negative T waves over the left chest were demonstrable in only one of the tracings.

These electrocardiographic abnormalities simulate those found among other primary myocardial diseases of infancy. On the basis of T-wave changes alone, glycogen storage disease cannot be differentiated with certainty from such lesions as primary endocardial fibroelastosis, aberrant origin of the left coronary artery arising from the pulmonary artery, interstitial myocarditis, and medial necrosis of the coronary arteries. However, study of the QRS complexes offers some information which is useful in attempting to differentiate the various entities in this group. For instance, in most cases of primary endocardial fibroelastosis and in all instances of aberrant origin of the left coronary artery arising from the pulmonary artery, the electrocardiogram should provide evidence of isolated left ventricular hypertrophy. A deep Q wave in Lead I and reciprocal changes in the S-T segments in Leads I and III may be present in the latter anomaly and should provide a means for differentiating these two conditions from each other. Glycogen storage disease

of the heart and interstitial myocarditis are conditions in which the myocardium is diffusely and uniformly involved. Hence evidence of isolated left ventricular hypertrophy would not be anticipated in these two entities; evidence of biventricular cardiac enlargement is to be expected. The presence of generalized muscle weakness in glycogen storage disease should permit its differentiation from interstitial myocarditis.

was also within normal limits at the time of birth but was found to be enlarged on the twentieth day.

At least two roentgenograms were available for review in each of the five infants included in this report; the earliest film taken at the age of two months and the latest at seven months. The cardiac silhouette was strikingly similar among the five patients. In all instances, the cardiac shadow was moderately enlarged with

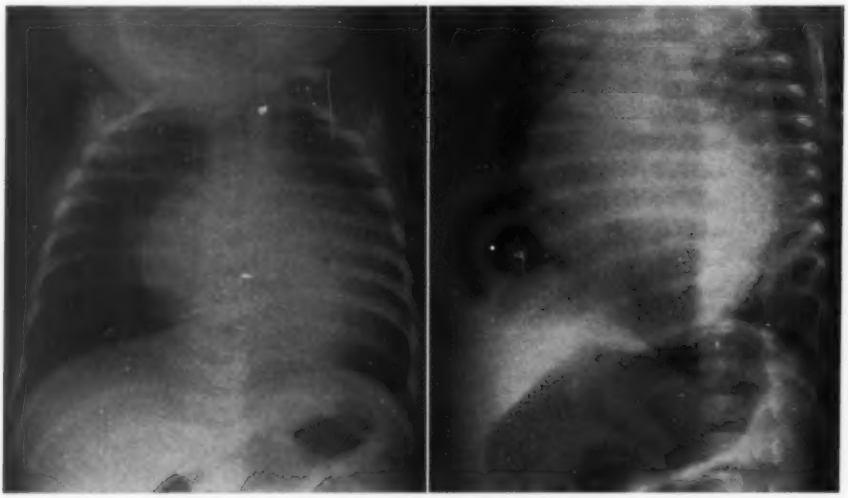

Fig. 2.—Roentgenograms of the chest taken in the anteroposterior and left anterior oblique views at the same time and from the same patient, as the electrocardiogram shown in Fig. 1, showing a moderate degree of cardiac enlargement with a globular cardiac contour.

Landing, Villee, and Nadas[14] made serial electrocardiographic observations in a patient with glycogen storage disease of the heart beginning at birth. A normal tracing was obtained at birth; this became abnormal between the tenth and twentieth day. The infant died at the age of one month and demonstrated the typical pathologic findings of glycogen storage disease of the heart. In this same infant the heart size on roentgen study

a rounded or globular contour in all views, particularly the anteroposterior and left anterior oblique (Fig. 2 and 3). The cardiac enlargement in each case was of a diffuse nature with no specific chamber enlargement demonstrable. This feature may provide assistance in the differentiation of this condition from some of the other primary myocardial diseases of infancy, especially from those conditions in which left ventricular enlargement

usually predominates, e.g., aberrant origin of the left coronary artery from the pulmonary artery and endocardial fibroelastosis. Among the five patients presented here, a moderate degree of cardiac enlargement was the rule; none showed massive and only one showed slight cardiac enlargement. The heart showed little change in size during the period of observation which ranged up to two months. Neither the pulmonary artery segment nor the peripheral vascular markings were especially prominent, although the problem of differentiating pulmonary infection from congestive heart failure arose in one case. In four of the five patients, pulmonary infection and/or atelectasis were present, usually involving the left lower lobe. Aspiration was thought to play a major role in the development of these pulmonary complications although cardiac enlargement with bronchial compression may also have been a factor. No pleural fluid was observed.

The diagnosis most commonly made at the time of admission or at the time of discovery of definite muscle weakness was amyotonia congenita or Werdnig-Hoffmann's disease. In no instance was the initial impression that of heart disease. In two instances the sluggish appearance of the baby with a large projecting tongue and flabby musculature suggested cretinism and/or mongolism. Two of the infants were given Prostigmin in order to rule out the diagnosis of myasthenia gravis; they showed no response. In some instances the cardiac involvement only became evident when

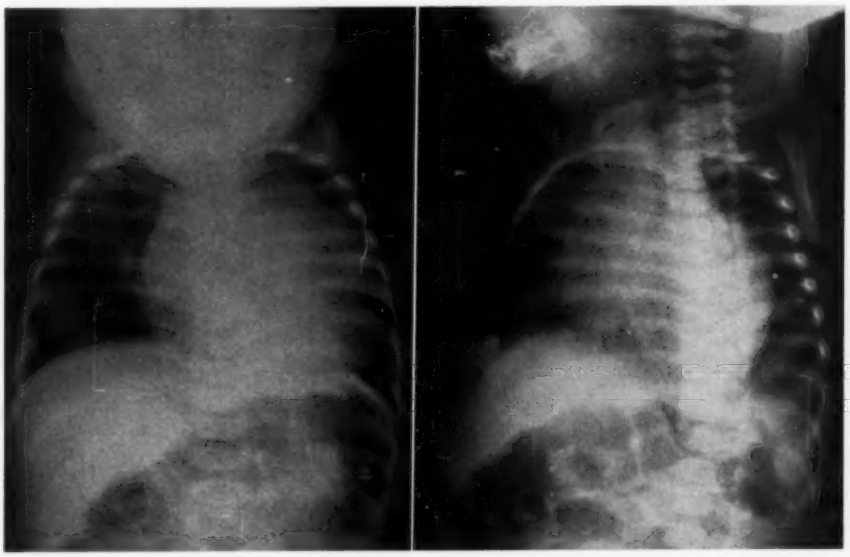

Fig. 3.—Roentgenograms of the chest in the anteroposterior and left anterior oblique views from a 5-month-old infant who died two months later from glycogen storage disease of the heart and skeletal muscles. Note similarity of general cardiac contour on comparison with Fig. 2. Also, in the anteroposterior view, the triangular-shaped double density appearing within the cardiac shadow is probably atelectasis of the left lower lobe.

a roentgenogram and/or electrocardiogram was recorded. The diagnostic problem was best resolved by carrying out a skeletal muscle biopsy. In each of our four cases examined in this way the muscle fibers showed vacuoles containing material with the staining characteristics of glycogen. Generalized muscle weakness was clinically evident at this time in all four instances. The absence of abnormal liver function tests, a normal response to epinephrine, and no response to Prostigmin were also useful indirect or negative contributions to the diagnosis.

In the course of the diagnostic investigation of the five infants included in this report, a host of laboratory tests were carried out. The results of these tests were similar to those found in the case described above and in those previously reported in patients with this disease; a mild normochromic anemia, normal routine urinalyses free of excessive sugar and acetone, normal response of blood sugar levels to epinephrine administration, normal liver function tests and blood chemistry studies. In addition, a few less commonly performed studies were carried out which are worthy of mention even though negative results were also obtained. Electromyographic recordings from the flexor digitorum sublimus of one infant showed normal motor unit potentials of decreased amplitude and decreased frequency consistent with a myopathy. There was no evidence of abnormal electrical activity such as might be associated with an intrinsic neurological condition. Chronaxie determinations from arm and leg muscles were normal, indicating no evidence of denervation. Ellis[15] earlier reported a normal response to faradic current stimulation. The serum glycogen level was determined in one case to be 8.16 mg. per cent; normal subjects tested simultaneously demonstrated serum glycogen levels of 20 to 25 mg. per cent. In one patient an electroencephalogram was reported to show no evidence of cerebral dysrhythmia. A normal ventricular system was also demonstrated in this patient on pneumoencephalography.

Specimens of skeletal and cardiac muscle from two patients were studied in the laboratory of Dr. Gerty T. Cori. The findings in one case are included in the case above. In the other instance the glycogen structure was also reported to be normal; an average 37 per cent of the glucose residues of each glycogen molecule were in the outer branches, which is within the range of "normally occurring" glycogens. No enzyme deficiency was found.

The pathologic changes, both gross and microscopic, found in this disease have been adequately described.[16] In the five specimens available for review, obvious cardiac enlargement was present in all instances, the average cardiac weight being 108 grams as compared to 36 grams for comparable normal infants.[17] In all instances the average left ventricular wall thickness was three times greater in these specimens than the average right ventricular wall thickness. The relationship of the left and right ventricular wall thicknesses was approximately the same as is seen normally at a comparable age, suggesting that all portions of the heart muscle are evenly and diffusely involved. No additional gross congenital cardiac anomalies were noted in any of the specimens.

The microscopic examination of the myocardium showed fibers of increased size with prominent, irregular, hyperchromic nuclei. The sarcoplasm was displaced to the periphery of the cells by a wide clear zone of material which had the staining characteristics of glycogen.

The finding of glycogen deposition on microscopic examination of the myocardium is not uncommon and is per se not specific for any one disease process. Mowry and Bangle[18] found glycogen in the myocardium of six of thirty-three infants dying of variable causes unrelated to any type of glycogen storage disease. The presence of glycogen in the myocardium of diabetic patients is also well recognized.[19] Thus, the finding of diffusely deposited glycogen in the myocardium is not in itself specific for either the hepatic or cardiac type of glycogen storage disease. In general, a quantitatively greater degree of infiltration will be found in the heart in the cardiac form as compared to the hepatic form of glycogen storage disease, although considerable deposition occurs in all organs of the body in both forms. Localized accumulations of glycogen in the myocardium are also known to occur and have been variously referred to as solitary and multiple cardiac rhabdomyomatosis, congenital glycogenic tumors of the heart, congenital nodular glycogenic degeneration of the myocardium, and by other titles.[20, 21, 22] These lesions are apparently not diseases of deposition of glycogen but are considered to be either tumors or developmental malformations associated with some degenerative process. A variety of other congenital cardiac anomalies in which myocardial hypertrophy and perhaps myocardial ischemia are present may also be associated with the deposition of glycogen in the myocardium. In infants born of diabetic mothers and in infants dying of erythroblastosis fetalis,[5] glycogen storage in the myocardium has also been observed. Thus, the pathologic diagnosis of glycogen storage disease of the heart cannot be made on the basis of glycogen deposition in the myocardium alone.

SUMMARY

1. The clinical findings in five infants with glycogen storage disease of the heart and skeletal muscle system have been summarized. Emphasis has been placed upon the prominent role played by generalized muscle weakness and its complications rather than the cardiac manifestations in this entity.

2. The electrocardiographic findings in four patients with this disease are presented in detail because of the relative paucity of previously reported tracings.

3. Some problems pertaining to the differential diagnosis, both clinical and pathologic, of glycogen storage disease of the heart and skeletal muscle system have been discussed.

We are indebted to Dr. Gerty T. Cori of St. Louis, Missouri, for the chemical analysis of tissue specimens carried out in two cases.

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FURTHER STUDIES ON THE CARDIOVASCULAR STATUS OF NORMAL NEWBORN INFANTS

IV. Effect of Adrenaline, Acetylcholine, 10 Per Cent Oxygen, and 100 Per Cent Oxygen on the Electrocardiogram

Claude Dupuis, M.D.,* Bracq Dupuis, M.D.,* Forrest H. Adams, M.D.,**
John Lind, M.D., and Tuomas Peltonen, M.D.

INFORMATION accumulated recently[1-6] indicates that the cardiovascular system of the normal newborn infant adjusts gradually over a period of several days rather than within minutes after birth as previously supposed.[7] The change from the fetal type of circulation to the newborn circulation is probably brought about by the following factors: an increase in systemic resistance; a decrease in pulmonary resistance; an increase in the arterial oxygen saturation; and other less well-defined factors.[8] Associated with these fundamental changes in the cardiovascular system is the presence of a large left-to-right shunt through the ductus arteriosus at rest[2, 5, 6] and a right-to-left shunt with crying[1, 4] and right ventricular and pulmonary artery hypertension.[5, 6] During this period of adjustment, the newborn infant's cardiovascular system responds to adrenaline and noradrenaline with an increase in right ventricular and pulmonary artery pressure; and adrenaline produces a tachycardia whereas noradrenaline produces a bradycardia.[9] Acetylcholine, 100 per cent oxygen, and 10 per cent oxygen with 90 per cent nitrogen appear to produce no significant effect on the right ventricular pressure of such infants.[9] These responses and findings in the normal newborn infant have been found to be somewhat different from those obtained in newborn animals.[10, 11]

The complexity of direct measurement of right heart pressures, shunts, and resistance suggests the need for simpler methods of measuring these changes. For these reasons, it seemed of interest to evaluate the role of the electrocardiogram in such studies. Ziegler[12] has recently reported the electrocardiographic changes during the first few hours and days of life as part of an over-all survey of the electrocardiographic findings in normal infants and children. In this connection, James[13] has suggested that the T wave in unipolar Lead V_1 may reflect in part the pressure in the right ventricle and pulmonary artery.

This paper presents the results of an investigation on the effects of adrenaline, acetylcholine, 100 per cent oxygen,

From the Wenner-Gren Cardiovascular Research Laboratory, Norrtull's Hospital, Stockholm, Sweden; the Department of Pediatrics, University of California at Los Angeles; and the Cardio-Respiratory Research Unit, University of Turku, Finland.

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*From the Children's Clinic, Cite Hospitalière, Lille, France (Professor A. Bretton).

**Department of Pediatrics, University of California School of Medicine, Los Angeles 24, Calif.

and 10 per cent oxygen on the electrocardiogram in normal newborn infants ranging in age from birth to 9 days. Cardiac catheterization was not performed as a part of these investigations.

MATERIALS AND METHODS

All of the newborn infants studied in this report were selected after history and physical examination had demonstrated that each was free from cardiovascular disease. No heart murmurs were recorded on the phonocardiogram.

Group I consisted of 30 infants born in the University Hospital at Turku, Finland. Electrocardiograms were recorded daily for the first 3 to 4 days of life by use of the conventional techniques and leads recommended by Ziegler.[12]

Groups II and III were comprised of 25 infants each born in the Södrabarnbordhuset, Stockholm, Sweden. The 25 infants of Group II were under 24 hours of age and the 25 of Group III were between 5 and 9 days of age. This later age period was selected to compare with the former since it is thought that the major neonatal circulatory adjustments are completed by 5 days of age under normal circumstances.[5, 6] In these two groups of infants, the three standard biopolar, the three unipolar extremity, and unipolar Leads V_1 and V_5 were recorded in each.

Group IV consisted of 10 infants under 24 hours of age. In each infant, a base-line electrocardiogram was obtained, as mentioned, for Groups II and III. With the electrocardiogram recording unipolar Lead V_1, five of the infants (Group IVa) were given 50 μg of acetylcholine (2 intravenously and 3 intramuscularly) and a continuous recording was made for five minutes. In five other infants in this age period (Group IVb) 100 per cent oxygen was administered by a small hood for periods of 10 to 20 minutes during which time electrocardiographic tracings were periodically made of unipolar Lead V_1.

Group V consisted of 12 infants 5 to 10 days of age. As in Group IV, base-line electrocardiographic tracings were obtained in each. With the electrocardiogram recording unipolar Lead V_1, six of the infants (Group Va) were given 50 μg of adrenaline intramuscularly and a continuous recording was made for five minutes. In two infants, 97 and 98, a second dose of 100 μg of adrenaline was given, and followed similarly; two others 95 and 96 received only 100 μg of adrenaline. In four other infants (Group Vb) 10 per cent oxygen with 90 per cent nitrogen was administered by a small hood for 10 minutes during which time electrocardiographic tracings were periodically made of unipolar Lead V_1.

All of the electrocardiograms were taken with a direct writing apparatus of the "jet" type (Elema Mingograph) using small electrodes. The concentration of the gas mixtures entering the baby was checked in each case with a Beckman oxygen analyzer, the sampling tip of which was placed at the nostrils. Readings were made periodically during each study. Measurements of the electrocardiographic tracings were made according to the recommendations of Ziegler.[12]

RESULTS

Table I summarizes the pertinent results obtained in the *longitudinal*

studies of the thirty infants in Group I ranging in age from birth to 4 days. Each infant with the age at the time of study is listed. There were 16 female infants and 14 male infants. All had normal weights and lengths. In 19 of the 33 infants, the electrocardiographic axis deviation decreased with time, but these variations were frequently slight and of little significance. All showed evidence of right ventricular hypertrophy as manifest by prominent RV_1 and SV_5. The T wave in V_1 was positive in all infants prior to 12 hours of age and positive in most up to 24 hours of age. After this time, TV_1 frequently became diphasic and then negative. There appeared to be no relationship between TV_1 and the axis deviation or RV_1 and SV_5. TV_5 was usually positive, but it was negative on six occasions, including 3 times in infant No. 20. The ventricular activation time of V_1 in all infants was 0.02 second or less.

Table II summarizes the pertinent results obtained in the *cross-sectional* studies of the 25 infants in Group II; all were under 24 hours of age. There were 13 male and 12 female infants; all had normal weights and lengths. They are arranged according to increasing age, the youngest was 1 hour and the oldest was 24 hours. The mean axis deviation was 130 degrees with a range of 105 to 170 degrees. As in Group I, all showed evidence of right ventricular hypertrophy as manifested by a prominent RV_1 and SV_5. The T wave in V_1 was positive in those infants under 12 hours of age. Between 12 and 24 hours of age there were 4 infants who had diphasic and 3 who had negative T waves in V_1.

Table III summarizes the pertinent results obtained in the *cross-sectional* studies of the 25 infants in Group III, all of whom were between 5 and 9 days of age. There were 16 male and 9 female infants; all had normal weights and lengths. They are arranged according to increasing age; the youngest was 5 days and the oldest was 9 days. The mean axis was 130 degrees with a range of 103 to 185 degrees. As in Groups I and II, all infants showed evidence of right ventricular hypertrophy. The T wave in V_1 was negative in 20 infants and slightly diphasic in 5 infants. The major diphasic component in this later group was always negative.

The results of the administration of 50 μg of acetylcholine to five infants are summarized in Table IV. These infants ranged in age from 5 hours to 30 hours. In two, the drug was given intravenously and in three it was given intramuscularly in the arm. Although some inconsistent changes in the heart rate occurred, no other effects were observed on the electrocardiogram including the amplitude of the T wave in V_1 which was positive in each case.

The results of breathing 100 per cent oxygen obtained in five infants for ten to twenty minutes are summarized in Table V. These infants were between 1 hour and 25 hours of age. The heart rate frequently decreased slightly but not invariably. The T wave in V_1 was positive in all prior to, during, and following the procedure. The oxygen appeared to have no effect on it or any other part of the electrocardiogram. All of the babies appeared agitated and 3 infants vomited.

Group V contained those infants 5 to 10 days of age. In six of these, 50 μg of adrenaline was given intramuscularly, two of whom received a second

TABLE I. LONGITUDINAL ELECTROCARDIOGRAPHIC FINDINGS IN 30 NORMAL NEWBORN INFANTS FROM BIRTH TO 4 DAYS OF AGE (GROUP I)

INFANT	SEX	WEIGHT (GRAMS)	LENGTH (CM.)	AGE (HOURS)	AXIS DEVIATION (DEGREES)	HEART RATE PER MIN.	RV_1 (MM.)	SV_1 (MM.)	TV_1 (MM.)	RV_5 (MM.)	SV_5 (MM.)	TV_5 (MM.)
1	F	3,000	50	3	140	108	15	10	2	4	19	−1
												+1
				27	128	106	9	4	−2	6	18	1
				56	112	108	12	11	−2	3	10	2
2	F	3,000	50	1	132	139	6	10	2	10	8	2
				25	130	142	8	9	2	8	12	2
				25	128	160	8	4	−1	7	12	2
3	M	3,250	50	13	135	142	10	2	7	10	11	1
				25	148	142	13	7	−2	3	7	1.5
									+1			
				49	118	132	10	7	−3	15	12	0.5
4	F	3,900	50	12	125	110	10	3	2	12	6	1
				36	120	100	8	3	−2	15	7	1
				60	110	122	5	0	−2	10	12	3
5	M	3,500	52	8	130	118	11	8	1	6	7	1
				31	150	144	11	9	2	8	20	2
				55	162	122	13	4	−1	11	17	1
									+1			
6	F	3,470	50	12	130	122	10	8	−2	12	9	1
				36	115	148	12	9	−2	14	7	1
				60	108	136	7	3	−2	8	3	2
7	F	4,250	52	22	130	135	10	10	−1	4	11	1
									+1			
				46	124	130	10	8	−2	3	8	0.5
				70	122	125	11	16	−2	5	12	2
8	M	3,580	51	25	152	142	14	0	−1	11	30	3
									+1			
				49	145	140	12	0	−3	8	15	2
				36	128	130	6	0	−1	16	24	2
9	M	3,600	51	10	114	110	5	11	1	4	5	0.5
				34	110	120	10	15	−2	5	9	2
									+1			
				58	112	108	5	11	−1	7	8	2
									+1			
10	F	4,300	54	23	152	118	8	3	−2	5	15	1
				47	180	118	12	8	−2	3	12	2
				71	128	142	7	3	−2	5	12	2

11	F	3,200	51	18	152	130	9	3	1	10	12	2
				42	158	135	12	4	−1 +1	5	15	1
				65	145	124	15	3	−1 +1	12	15	2
12	F	4,300	54	20	125	138	10	8	3	5	10	1
				44	124	148	12	2	−1 +1	7	14	1
				68	135	132	8	2	−2	10	18	1
13	F	3,100	51	17	118	112	20	2	1	13	8	2
				39	115	108	8	1	−1 +1	14	12	2
				63	104	118	20	2	−2	15	7	1
14	M	3,780	52	25	172	148	9	4	2	8	13	2
				49	155	150	22	13	−2 +2	9	20	2
				74	150	130	17	9	−3 +1	7	20	2
15	M	3,500	51	26	175	112	14	2	2	5	15	1
				50	170	150	12	8	−3	5	12	2
				75	158	124	14	2	−3	5	18	2
16	F	3,100	50	27	102	140	9	4	1	17	30	2
				56	118	130	10	2	1	12	22	2
				80	118	148	18	5	−3 +1	14	18	2
17	M	4,080	51	35	150	140	8	0	−1 +1	8	15	2
				58	160	135	8	2	−2	7	12	1
				82	152	134	10	1	−2	5	12	2
18	F	3,450	51	8	132	118	15	1	2	14	15	1
				32	128	132	18	11	−2 +2	8	14	1
				57	120	132	20	2	−2	12	16	1
19	F	2,420	45	25	120	110	8	5	−2	14	5	1
				49	112	148	10	12	−4	10	14	2
				72	106	140	10	8	−5	5	8	2
20	F	3,620	31	26	112	148	8	0.5	1	21	13	1
				50	105	135	9	4	1	21	12	1
				73	102	148	10	4	1	28	13	1

TABLE I—CONT'D

INFANT	SEX	WEIGHT (GRAMS)	LENGTH (CM.)	AGE (HOURS)	AXIS DEVIATION (DEGREES)	HEART RATE PER MIN.	RV_1 (MM.)	SV_1 (MM.)	TV_1 (MM.)	RV_2 (MM.)	SV_2 (MM.)	TV_2 (MM.)
21	M	3,240	51	27	118	142	12	8	1	5	15	2
				50	120	154	15	8	−1	12	30	12
									+1			
				74	120	152	13	2	−4	12	17	3
22	F	4,320	52	37	122	148	8	5	−1	9	24	1
				60	134	128	15	9	−2	8	13	1
				84	134	165	15	5	−2	10	15	0.5
23	M	4,150	54	34	170	122	7	4	−2	2	9	1
									+1			
				68	180	140	12	9	−3	5	9	1
				92	158	130	14	7	−2	6	15	12
24	M	3,540	53	46	165	135	23	4	−2	6	19	12
									+1			
				70	170	132	30	8	−3	3	9	2
				94	165	138	20	5	−5	5	11	12
25	M	2,450	45	22	125	136	12	5	−2	10	12	1
				46	118	156	12	6	−2	11	14	1
				72	110	152	7	1	−1	9	7	12
26	F	4,530	55	6	155	145	9	5	3	2	10	12
				53	138	142	10	1	−2	4	15	3
				77	152	140	15	3	−3	2	18	2
27	F	3,770	51	6	122	132	11	1	2	10	13	1
				30	124	138	11	0	2	7	4	1
				75	130	124	9	2	−2	4	3	2
									+1			
28	M	4,000	52	13	120	122	7	5	2	5	3	1
				38	170	120	15	5	−4	10	11	2
				85	180	152	15	3	−3	5	10	12
29	M	3,230	49	26	152	145	19	10	−3	10	15	12
									+2			
				44	155	152	20	6	−3	14	9	2
									+1			
				118	132	148	10	4	−3	20	11	−2
30	M	3,440	50	44	152	150	12	0	−2	3	11	1
				91	165	136	13	1	−1	11	13	3
				103	168	124	10	0	−2	5	10	3

TABLE II. CROSS-SECTIONAL ELECTROCARDIOGRAPHIC FINDINGS IN 25 NORMAL NEWBORN INFANTS UNDER 24 HOURS OF AGE (GROUP II)

INFANT	SEX	WEIGHT (GRAMS)	LENGTH (CM.)	AGE (HOURS)	AXIS DEVIATION (DEGREES)	HEART RATE PER MIN.	RV_1 (MM.)	SV_1 (MM.)	TV_1 (MM.)	RV_5 (MM.)	SV_5 (MM.)	TV_5 (MM.)
31	M	3,500	50	1	120	130	18	5	3	6	15	1
32	M	3,130	50	2	140	120	12	0	2	1	17	1
33	M	3,710	49	3	138	115	9	5	1	15	15	2
34	F	3,000	50	4	120	150	7	1	5	15	19	4
35	M	3,800	51	5	155	122	12	0	1	6	5	1
36	F	3,220	50	5	150	132	10	9	2	22	15	3
37	F	3,770	51	10	118	132	15	0	4	12	5	1
38	F	2,945	49	11	150	130	10	11	2	2	4	0.5
39	M	3,380	50	11	115	108	12	25	4	7	8	1
40	F	3,500	50	12	105	150	15	13	5	8	5	-1
41	M	3,520	50	12	144	120	13	2	-2 +1	8	8	1
42	M	3,420	50	14	122	114	15	13	3	11	23	1
43	M	3,430	50	15	120	110	15	10	2	8	9	1
44	F	3,300	48	15	124	120	10	4	2	11	9	1
45	F	2,730	50	15	120	132	9	20	-1 +1	10	18	1
46	F	2,500	49	15	115	145	15	5	-1	10	10	-2
47	M	3,080	47	15	120	122	13	12	3	10	12	2
48	F	3,500	51	18	122	130	13	7	-2	15	11	+1
49	F	3,150	51	19	112	136	10	10	-4	8	7	2
50	M	3,400	51	20	152	138	9	3	2	7	18	1
51	M	3,800	51	22	130	135	9	8	1	4	19	2
52	F	3,500	50	22	110	115	16	22	-2 +2	16	16	1
53	M	3,240	50	23	170	130	13	4	2	17	25	2
54	M	3,300	50	23	120	105	12	4	1	10	5	1
55	F	3,570	51	24	125	145	16	9	-1 +1	15	15	-2

TABLE III. CROSS-SECTIONAL ELECTROCARDIOGRAPHIC FINDINGS IN 25 NORMAL NEWBORN INFANTS BETWEEN 5 AND 9 DAYS OF AGE (GROUP III)

INFANT	SEX	WEIGHT (GRAMS)	LENGTH (CM.)	AGE (DAYS)	AXIS (DEGREES)	HEART RATE	RV_1 (MM.)	SV_1 (MM.)	TV_1 (MM.)	RV_5 (MM.)	SV_5 (MM.)	TV_5 (MM.)
56	M	3,590	50	5	152	120	16	8	−3 +2	10	5	1
57	F	3,000	50	5	110	108	7	4	−3	15	12	2
58	M	3,980	51	5	154	110	16	5	−2	15	10	2
59	M	3,600	51	5	132	130	20	7	−5	5	15	3
60	F	2,760	49	5	103	140	15	12	−6	12	9	2
61	M	4,300	52	5	148	142	12	14	−2	6	12	3
62	F	3,270	50	5	160	132	14	5	−5	11	15	1
63	F	3,000	50	5	125	135	9	7	−5	11	10	0
64	M	2,850	48	5	170	128	11	4	−3	13	15	3
65	F	2,760	50	5	130	135	16	8	−4	20	8	−2
66	M	3,430	50	5	110	134	20	7	−6	12	12	−1
67	M	3,980	52	6	128	125	15	3	−2	13	14	−2
68	M	3,250	50	6	145	132	6	5	−2	4	16	1
69	M	4,250	51	6	126	118	13	10	−2 +1	14	12	2
70	M	3,720	51	6	180	152	23	15	−6 +3	12	18	3
71	F	3,700	51	6	125	144	13	10	−5	6	9	1
72	M	4,210	52	6	175	134	12	3	−2	5	14	3
73	M	4,570	52	6	144	128	13	5	−4	13	16	1
74	F	3,620	50	6	110	135	14	17	−3 +1	15	8	2
75	M	3,800	51	6	155	150	9	6	−4	8	16	3
76	M	4,280	51	7	128	145	20	17	−5	17	13	2
77	F	2,500	49	8	122	170	10	9	−5	17	10	2
78	F	3,200	51	8	158	144	9	1	−3	13	15	2
79	M	3,300	50	8	185	148	9	4	−5	7	18	1
80	M	3,000	49	9	110	106	8	10	−2 +1	10	10	3

TABLE IV. EFFECT OF 50 μG ACETYLCHOLINE IN 5 NORMAL INFANTS
(Group IVa)

INFANT	81			82			83			84			85		
AGE (HOURS)	5			15			5			30			16		
ROUTE	I.M.			I.M.			I.M.			I.V.			I.V.		
TIME (SECONDS)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)
0	135	–	2	105	–	2	120	–	2	135	–	3	110	–	3
15	135	0	2	105	0	2	128	+7	2	135	0	3	110	0	3
30	105	–23	2	105	0	2	120	0	2	140	4	3	110	0	3
45	135	0	2	105	0	2	–	–	–	135	0	3	110	0	3
60	135	0	2	140	33	2	115	–4	2	135	0	3	105	–4	3
120	105	–23	2	135	28	2	115	–4	2	130	–4	3	105	–4	3
180	130	–4	2	115	9	2	120	0	2	135	0	3	105	–4	3
300	145	8	2	105	0	2	128	+7	2	130	–4	3	105	–4	3

TABLE V. EFFECT OF 100 PER CENT OXYGEN ADMINISTERED BY HOOD TO 5 NORMAL INFANTS
(Group IVb)

INFANT	86			87			88			89			90		
AGE (HOURS)	11			23			1			20			25		
TIME (MINUTES)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)
0	110	–	4	125	–	4	125	—	2	140	—	2	100	—	4
2	105	–4	4	120	4	4	120	–4	2	135	–3	2	80	–20	4
4	100	–9	4	120	–4	4	125	0	2	120	–14	2	90	–10	4
6	100	–9	4	135	8	4	125	0	2	130	–7	2	85	–15	4
8	75	–32	4	125	0	4	120	–4	2	130	–7	2	95	–5	4
10	110	0	4	135	8	4	115	–8	2	120	–14	2	85	–15	4
12	96	–	–	115	–8	4	125	0	2	125	–10	2	80	–20	4
14	90	–18	4	125	0	4	125	–4	2	120	–14	2	106	6	4
16	100	–9	4	125	0	4	120	–4	2	135	–3	2	82	–18	4
18	110	0	4	130	4	4	120	–4	2	135	–3	2	84	–16	4
20	120	9	4	130	4	4	—	—	–	—	—	–	132	32	4

TABLE VI. EFFECT OF 50 AND 100 μG OF ADRENALINE ON 8 NORMAL INFANTS
(Group Va)

INFANT	91			92			93			94			95		
AGE (DAYS)	5			5			6			5			5		
DOSE	50 μg			50 μg			50 μg			50 μg			100 μg		
TIME (SECONDS)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)
0	135	—	−4	125	—	−5	120	—	−3	110	—	−3	176	—	−5
15	150	11	−4	175	40	−4, d +4	135	13	−3, d +2	165	50	−3	176	0	−5, d +5
30	140	4	−5, d +2	175	40	−4, d +7	120	0	−4, d +2	165	50	−4	170	−3	−3, d +3
45	150	11	−4, d +1	180	44	−4, d +7	105	−13	−2, d +1	165	50	−7	165	−6	−3, d +3
60	150	18	−5	180	44	−6	105	−13	−3, d +1	105	−4	−2, d +3 ← E.	100	−42	5
120	150	11	−5 N.E.	180	44	−5	90	−25	−3, d +1	100	−8	−3, d +2	88	N.R. → −50	−4, d +3
180	140	4	−4	120	−4	−5	110	−9	−3	110	0	−5	95	−45	−5, d +2
300	135	0	−4	150	20	−6, d +7	120	0	−3	90	−17	−8 } Big.	110	−32	−5

INFANT	96			97			97			98			98		
AGE (DAYS)	6			9			9			10			10		
DOSE	100 μg			50 μg			100 μg			50 μg			100 μg		
TIME (SECONDS)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)
0	150	—	−5	105	—	−3, d +1	140	—	−3	170	—	−3	170	—	−3
15	—	—	—	165	52	−5, d +1	160	14	−5	180	6	−3	150	−12	−3
30	—	—	—	150	43	−6, d +1	180	28	−5	180	6	−4	190	12	−3
45	—	—	—	145	40	−5, d +2	160	14	−4, d +1	165	−3	−6	170	0	−3
60	160	7	−7, d +1	150	43	−8, d +1	155	10	−4, d +1	185	8	−8	150	−12	−3, d +2
120	155	3	−2, d +2	135	28	−7, d +1	110	−22	−3, d +1	150	−12	−3, d +2 ← N.E.	140	N.E. → −18	−3, d +2
180	155	3	−3, d +2	135	28	−7, d +1	100	−29	−4, d +1	180	6	−6	120	−30	−3
300	—	—	—	114	9	−6	140	0	−7	180	6	−3	135	−20	−4

Key: N.R. = nodal rhythm. E. = extrasystole. Big. = bigeminal rhythm. N.E. = nodal extrasystoles. d = diphasic.

injection of 100 μg. The results of these studies are summarized in Table VI. Commonly there was an increase in heart rate of variable degree; however, a few showed bradycardia due to disturbances of rhythm. There were 2 instances of nodal rhythm, 3 of nodal extrasystoles, and 1 of bigeminal rhythm. In all instances, changes occurred in TV_1, which prior to administration of adrenaline was negative. In one instance, it became positive and in the others it became diphasic. The infants responded by manifesting agitation and early suffusion followed by paleness and tachypnea.

Ten per cent oxygen in 90 per cent nitrogen was administered by hood for 10 minutes to four infants of Group Vb. The results are summarized in Table VII. Three were 6 days of age and one was 8 days old. All infants became cyanotic and somnolent. The heart rate increased somewhat, but not consistently. No changes were observed on the electrocardiogram including TV_1.

TABLE VII. EFFECT OF 10 PER CENT OXYGEN ADMINISTERED BY HOOD TO 4 NORMAL INFANTS (Group Vb)

INFANT	99			100			101			102		
AGE (DAYS)	6			6			6			8		
TIME (MINUTES)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)
0	150	—	−3	125	—	−3	105	—	−3	150	—	−3
2	160	7	−3	105	−16	−3	120	15	−3	150	0	−3
4	162	8	−3	100	−20	−3	118	13	−3	172	14	−3
6	162	7	−3	120	−4	−3	120	15	−3	153	2	−3
8	166	10	−3	140	12	−3	125	20	−3	150	0	−3
10	165	10	−3	105	−16	−3	122	17	−3	150	0	−3

DISCUSSION

The results of these studies on the electrocardiographic changes with age in the normal newborn infant are in general agreement with the earlier reported findings of Ziegler.[12] Specifically the T wave in unipolar Lead V_1 was regularly positive under 12 hours of age and negative or diphasic after 5 days of age. The transition between these two phases was gradual and took place over the same time interval that the pulmonary hypertension normally disappears.[5, 6] Evidence of right ventricular hypertrophy, however, persisted throughout this entire period without significant change. Administration of adrenaline to infants with presumably normal pulmonary artery pressures frequently produced changes in the T waves of the electrocardiogram similar to those found in infants *with* pulmonary hypertension.

Earlier attempts by us to reduce the pulmonary hypertension in infants under 24 hours of age by administration of acetylcholine or breathing 100 per cent oxygen were unsuccessful.[9] The negative results in these electrocardiographic studies are consistent with the earlier observations. This lack of effect of acetylcholine on the pulmonary hypertension of newborn infants is in constrast to its effect in adults[14-16] and animals[10, 11] with pulmonary hypertension. The negative effect of 100

per cent oxygen in these infants is also in constrast to its effect in some adults with pulmonary hypertension.[17]

The inability to alter significantly the electrocardiographic pattern of newborn infants by administration of either 10 per cent or 100 per cent oxygen speaks against acute anoxia or anoxemia as a common cause of the findings.[18]

In spite of the results of these studies and of those reported previously, it is still difficult to make any positive statements regarding the nature of the pulmonary hypertension in the normal newborn infant. Further studies are indicated.

SUMMARY

The electrocardiographic changes in the normal newborn infant during the first 10 days of life were investigated. Thirty infants were studied longitudinally and seventy-two were studied cross-sectionally. The physiologic response of certain of the latter group of infants to administration of 10 per cent and 100 per cent oxygen by mask and to adrenaline and acetylcholine was measured recording unipolar Lead V_1.

Changes with age reported earlier by Ziegler were confirmed. Alteration of the T wave in V_1 took place over the same time interval that the pulmonary hypertension normally disappears. In older infants, administration of adrenaline produced changes in the T wave of V_1 similar to those found in younger infants who normally have pulmonary hypertension.

Administration of 100 per cent oxygen to the younger infants and 10 per cent oxygen to the older infants produced no significant alteration in the electrocardiographic tracing of V_1, other than minor changes in the rate. Likewise, administration of acetylcholine to the younger infants produced no significant change in the pattern.

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Piece of Tin in the Windpipe. Laryngo-tracheotomy.—Dr. Paul F. Eve records (*Nashville Journ. Med. and Surg.*, Sept., 1857) the case of a negro boy, three years of age, which strongly illustrates the occasional great power of endurance of the human system. The patient two days before being taken to Dr. E., "while attempting to whistle with a small strip of tin in his mouth, fell backwards out of a piazza and inhaled it into his windpipe. This was followed by instant and persistent embarrassment to respiration, loud rhonchus, loss of voice, or rather its reduction to a whisper, and some slight hemorrhage. The family physician not having relieved the patient by an emetic, inversion of the body, etc.," directed the boy to be taken to Nashville. Being satisfied from the symptoms that there was a foreign body in the windpipe, Dr. E. decided to operate. Accordingly, on the 13th June, four days after the accident, Dr. E. opened the larynx, and then the trachea, and made "diligent search" for the foreign substance. The larynx was twice wiped out by sponges carried through the wound and brought out of the mouth, and the trachea and bronchi carefully and cautiously explored with probes and long forceps, but nothing special detected. There was an unusual amount of hemorrhage in the division of the soft parts, and ligatures were applied to each side of the isthmus of the thyroid body before its section. Dr. Bowling administered the anaesthetic agent (equal portions of ether and chloroform), while Drs. Jennings, Briggs, Wharton and others aided during the operation, which to any one who has never opened the windpipe of a fat child three years old, it would be unnecessary to say, was a tedious and embarrassing one.

The second morning, during a paroxysm of cough, a piece of tin, measuring seven-tenths of an inch in length, and three-twentieths in width, with sharp angles and edges, was ejected through the wound. It was smooth and polished upon its two surfaces, discolored, however, now by bloody mucus. Treatment, antiphlogistic, continued.

In a day or two the patient began to improve, and on the tenth day left for home.

TRUE HERMAPHRODITISM

Report of a Case

Walter Hughes, M.D., Cyrus C. Erickson, M.D., Walter Fleischmann, M.D., and James N. Etteldorf, M.D.
Memphis, Tenn.

THE first "hermaphrodite" was presented not in medical literature, but as an amazing creation in Greek mythology from the union of Hermes and Aphrodite. For hundreds of years this remarkable creature, with attributes of both male and female, was deified in romantic literature and the arts. It was not until the latter part of the nineteenth century that the subject was approached scientifically in medical literature.[1] Young's[2] classical monograph in 1937 presented 20 acceptable cases of true hermaphroditism that had appeared in the literature up to that time. A case reported by Gudernatsch[3] in 1911 was later accepted by Young. In 1944, McIver, Seabaugh and Mangels[4] reviewed 13 additional cases. Fischer, Lischer, and Byars,[5] in 1952, listed 14 subsequent cases and added one of their own. In 1956, Schwiebinger and Hodges[6] presented the fifty-fifth case of true hermaphroditism after mentioning 5 other acceptable cases. Considering 14 additional and recently reported cases,[7-19] the patient presented here apparently is the seventieth case of true hermaphroditism in the medical literature, and the eighteenth case of the lateral or alternating type.

From the Division of Pediatrics, College of Medicine, and Division of Pathology and Microbiology, University of Tennessee, and the Le Bonheur Children's Hospital, Memphis, Tenn.

Undoubtedly, this condition is much more frequent in occurrence than its appearance in medical archives would lead one to believe. We are aware of 3 cases of true hermaphroditism from other hospitals in Memphis that have not yet been published.[20, 21] Recently, Clayton, O'Heeron, and Smith[22] have published a case report. Most of the patients in the reported cases were not seen or diagnosed by a physician before adolescence and were thus subjected to the early psychologic trauma because of their anomaly. It is academic to point out that preventive therapeutics (medical, surgical, and psychologic) will produce more satisfying results when the correction of such a condition is accomplished before the patient reaches the adolescent period.

The case presented here is classified as the lateral or alternating type according to Hinman's[23] simplified grouping of three types of true hermaphroditism; they are:

1. *Bilateral:* testis and ovary on both sides, either separate or united as an ovotestis.

2. *Unilateral:* testis and ovary, either separate or united, on one side, with testis or ovary on the other.

3. *Lateral or Alternating:* testis on one side and ovary on the other.

CASE REPORT

History.—R. T., a 15-year-old Negro, was admitted to the Le Bonheur Children's Hospital on Jan. 23, 1956, because of enlargement of the breasts and abnormalities of the external genitalia.

The patient was born as the result of a normal pregnancy of a para iii gravida iv mother with an apparently uncomplicated delivery. At the time of birth, it was noted that the infant had ambiguous external genitalia which prevented definite assignment of sex. The infant was taken to a local physician soon after birth for a physical examination. Determination of chromosomal patterns was not available at that time. Since the genitalia resembled that of a male more than that of a female, the baby was given the name Robert and reared as a male. The patient remained quite healthy, at no time had signs or symptoms of electrolyte imbalance or other abnormalities, and grew and developed with a normal male physique.

At 6 years of age, the child started to school and was accepted as a male. Participating in sports and with male companionship, social adaptation was adequate throughout the childhood period.

At 12 years of age a definite deepening of the voice was apparent, erections of the small phallus were experienced, and sexual drives were oriented toward the female.

At 13 years of age, a routine blood examination by the Public Health Department revealed a positive test for syphilis and the patient was given antisyphilitic treatment. It was also during the thirteenth year that bilateral enlargement of the breasts was noted. The breasts continued to enlarge to a size that caused embarrassment to the patient. There was no history of bleeding from the perineal opening or abdominal cramping indicative of menarche.

The patient had 9 siblings, all of whom were well and had no apparent abnormalities.

Physical Examination.—The patient appeared to be a well-nourished and well-developed Negro boy measuring 5 feet and 9 inches in height (Fig. 1). The temperature, pulse, and blood pressure were normal. There was no beard visible. The thyroid was not enlarged to palpation. The breasts were enlarged bilaterally to the size of those of a 17- or 18-year-old girl and mammary ducts were palpated radiating from the nipples. No abnormalities of the heart and lungs were found.

Fig. 1.—Anterior view of patient revealing bilateral breast enlargement characteristic of a female with body build and external genitalia resembling a male.

The liver, spleen, and kidneys were not enlarged and no abnormal masses were found by abdominal palpation. A small amount of fine axillary hair was present. Pubic hair was present but did not extend onto the abdominal wall to a level that would permit the classification of male distribution. The phallus was 4 cm. in length with a

well-defined glans and a perineal hypospadias was equally visible (Fig. 2). A firm, movable mass, 2 cm. in diameter, was palpable near the external inguinal ring in the right scrotal sac which resembled the labium majus. A defect in the left inguinal ring permitted a small herniation, but no gonad could be palpated in the left labium. No prostate or cervix could be palpated through the rectum.

Fig. 2.—Close-up view of external genitalia illustrating small phallus, hypospadic urethra, and labia resembling scrotum.

Laboratory Findings.—The urinary excretion of 17-ketosteroids in 24 hours was 4.9 mg. (Table 1). Serum chloride was 108 mEq. per liter; NPN was 31 mg. per 100 c.c.; and a VDRL test was positive, 1:2 dilution.

Pyelograms and Osseus Development.—No abnormalities were apparent on the intravenous pyelogram or plain roentgenogram of the abdomen. Osseous development was normal for the patient's age. Chest and skull roentgenograms were not abnormal.

Endoscopy and Biopsy.—At endoscopy, the apparent urinary meatus in the perineum was found to be a common channel, and, about 2 cm. from the external orifice, there was a urethral orifice leading into a normal bladder. The channel extended posteriorly and superiorly into a blind pouch interpreted as vagina. In the most distant portion of the pouch, a small dimple could be seen which might have been a hypoplastic cervical os. On completion of the inspection, a vaginogram was made which outlined the vaginal pouch described.

Exploration of the right labium exposed a pearly white mass, approximately 1.5 cm. in diameter. The capsule of this oval nodule was incised with removal of a biopsy section for frozen section examination. The soft orange-tinted gray tissue underlying the firm outer covering had a stringy structure resembling testicular tissue.

Microscopic examination of the biopsy removed from this labial mass identified the structure to be atrophic testicular tissue (Fig. 3). Beneath the fibrous capsule the cross sections of seminiferous tubules typically appeared in islands or groups in a loose connective tissue stroma (Fig. 3). Interstitial cells in the loose stroma did not appear to be abnormal but appeared to be decreased in number. Evidence of spermatogenesis was absent; spermatogenic cells were not observed.

Adjacent to the testicular mass in the right labium was a smaller elongated structure with a passage extending from this toward the inguinal canal, but without a demonstrable communication into the abdominal cavity. Histologic study of the second mass proved this to be epididymis of essentially normal architecture (Fig. 4).

A large left inguinal hernia was present, but no masses or nodules were found in the left inguinal canal.

The hernial sac was opened and the adjacent peritoneal cavity was explored with a finger. A small, round mass was outlined, but its identity and anatomical attachments could not be established.

Exploratory Laparotomy.—On Feb. 2, 1956, an exploratory laparotomy was performed by Dr. George Livermore, Jr., and revealed a hypoplastic uterus, a grossly normal left Fallopian tube, and a mass resembling a left ovary in normal relation to the tube and uterus. Frozen section examination of the gonadal mass showed the

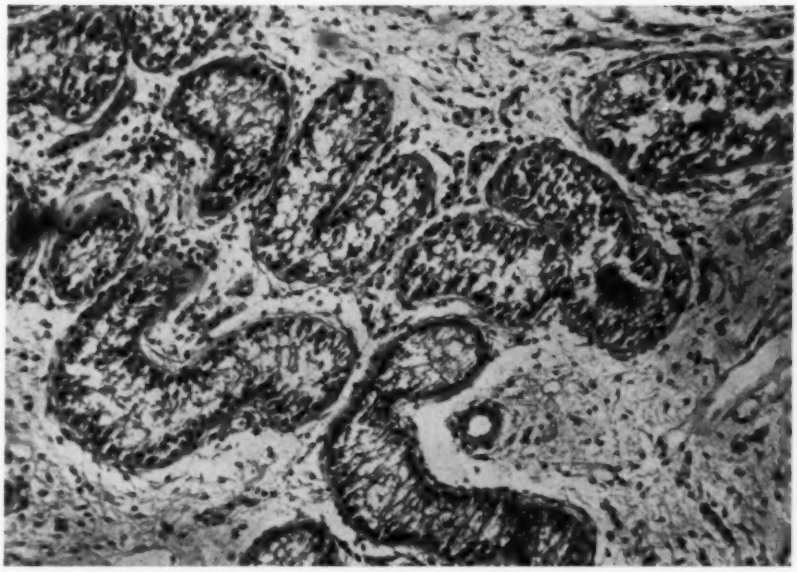

Fig. 3.—Biopsy section of atrophic testicular tissue from mass of right labium majus. The cells within the prominent basement membrane of the seminiferous tubules appear to be only of Sertoli type. (Hematoxylin and eosin; ×100; reduced ¼.)

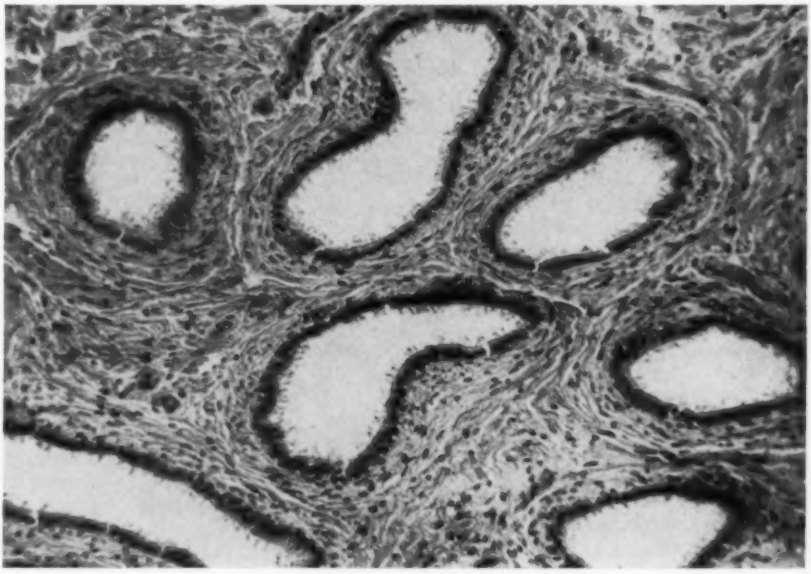

Fig. 4.—From right labial mass adjacent to testis. Normal epididymis. (Hematoxylin and eosin; ×100; reduced ¼.)

wedge biopsy to be tissue of ovarian structure. No other internal genital organs or masses were found; the uterus, left Fallopian tube and left ovary were removed (Fig. 5).

measuring up to 1 cm. in diameter. The thin fluid contents and lining walls of larger cysts were uniformly hemorrhagic as illustrated in Fig. 5. The microscopic examination revealed

Fig. 5.—Uterus, left tube, and left ovary, posterior view; uterine mass to right with left tube extending superiorly from left cornua to the free fimbriated end. The ovary has been hemisected to show the multiple large hemorrhagic follicular cysts.

Pathologic examination of uterus, left tube, and ovary: The bean-shaped uterus measured 5 by 2 by 2 cm., and on section had a small, poorly defined endometrial cavity. The dimpling of the blunt cervical end of the uterus did not communicate with the endometrial cavity. In the microscopic sections of the uterine wall, the estrogenic proliferative type endometrium is of especial interest. There is some variation in size and shape of columnar cell-lined endometrial glands, a few enlarged irregular cystic glands, and small polypoid projections into the endometrial cavity. The latter hyperplastic cystic changes are moderate (Fig. 6).

The Fallopian tube measured 8 cm. in length and was grossly and histologically normal.

The ovary measuring 3 by 2 by 2 cm. contained many thin-walled cysts a thick, dense, fibrous capsule without covering germinal epithelium. The cortex is made up of characteristic but fibrous ovarian stroma containing but few structures resembling primordial follicles. The greater portion of the ovary as illustrated (Fig. 5) is occupied by the large hemorrhagic follicular cysts. The larger follicular cysts are lined by thin or single layer of cuboidal granulosa or by fibrous-appearing theca; these cysts uniformly had prominent perifollicular hemorrhage with blood in adjacent stroma. Several small peripheral cysts in the cortex (Fig. 7) are lined by granulosa, several cells in thickness with rosette-like pattern and as in the follicle illustrated with peninsula-like accumulation of granulosa cells. Other small atretic follicles are lined by hyalinized compressed connective tissue cells and contain blood. Of interest are the

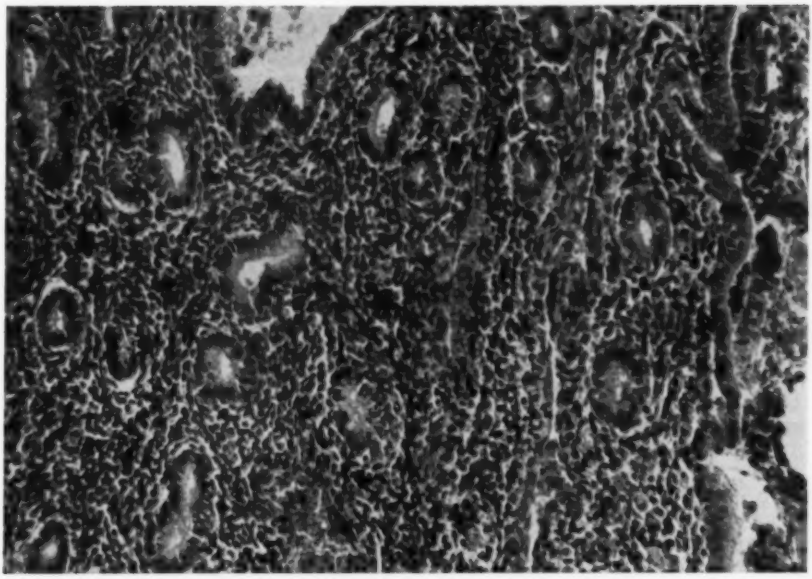

Fig. 6.—Proliferative endometrium. The endometrial cavity and surface epithelium is at the *right*. (Hematoxylin and eosin; ×100; reduced ¼.) A portion of one of large irregular cystic glands is shown at the *top* margin.

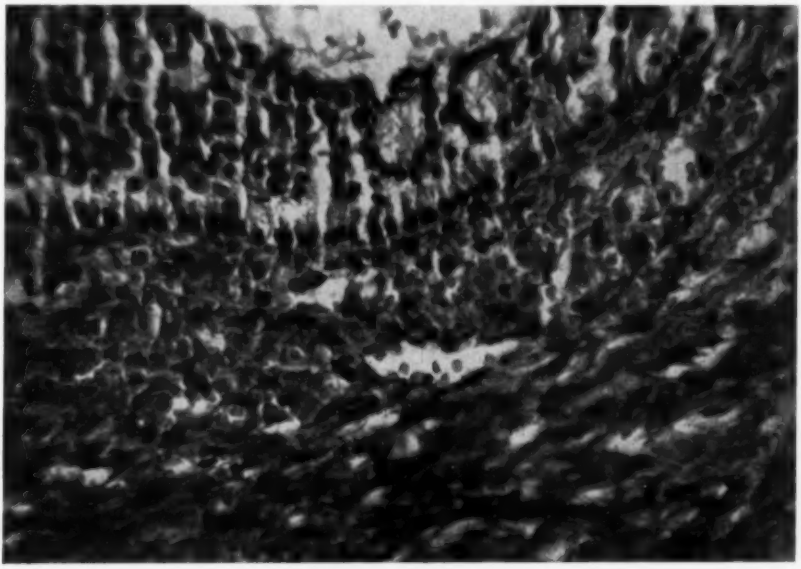

Fig. 7.—Section of ovary. Granulosa cell lining adjacent to cumulus-like prominence of cystic follicle. Multicelled granulosa lining present only in few of smaller peripheral cystic follicles. (Hematoxylin and eosin; ×200; reduced ¼.)

many very small double-layered wavy hyalinized structures considered to be remnants of obliterated atretic follicles.

Sex-chromatin studies: Skin specimens were examined from the left groin, right thigh, and left subscapular region for the nuclear sex chromosomal pattern by the method described by Moore, Graham, and Barr.[2] The nuclear chromatin masses described as typical of the sex chromatin pattern of female cells were not found in the skin from the several sites described. These examinations were considered as evidence indicating these specimens represented the male chromosomal pattern. Biopsy sites from the various quadrants of the body were chosen to test the possibility that one area might contain a male pattern and another the female. This was not found to be true.

Hormone studies: Unfortunately, complete hormonal studies were not obtained preoperatively; however, 4 months after removal of the ovary, the urinary excretion of follicle-stimulating hormone level was 110 mouse units per 24 hours.

TABLE I. TWENTY-FOUR-HOUR URINARY EXCRETION OF FOLLICULAR-STIMULATING HORMONE AND 17-KETOSTEROID

	FSH (MOUSE UNITS)	17-KETOSTEROID (MG.)
Preoperative		4.9
Postoperative		
4 mo.	110	
8 mo.	110	12.6
12 mo.	105	7.0

Eight months after this surgical procedure, the urinary 17-ketosteroid excretion was 12.6 mg. per day, and the follicle-stimulating hormone was still 110 mouse units. One year following the oophorectomy, the 17-ketosteroid content of the urine was 7.0 mg. in a 24-hour specimen and the follicle-stimulating hormone was 105 mouse units.

Before surgery the 17-ketosteroid excretion was 4.9 mg. per day. The ovary apparently was functioning, as evidenced by breast enlargement prior to oophorectomy and by the rather high follicle-stimulating hormone excretion during the postoperative period. An alternate explanation of the increase in FSH is a low androgen output of testicular origin during the postoperative period. A 17-ketosteroid output of 12 and 7 mg. per 24 hours in the postoperative period may be accounted for by adrenal androgen output.

Two months following hysterectomy, a bilateral mammoplasty was performed. Over an 8-month period, a 3-stage repair of the hypospadias was undertaken, producing a penile urethra. The vaginal cavity was not removed. No hormone therapy was deemed necessary.

According to the recommendation of Wilkins[25] and Money[26] and their coworkers, we can assume that serious psychologic complications were avoided through rearing this patient consistently as a boy, leaving no doubts as to his assignment to the male sex. When his breasts started to enlarge at the age of 12, his gender role was already firmly imprinted. The danger of changing the original decision as to assignment of sex in later childhood has been stressed recently by the above authors.

SUMMARY

1. A case of true hermaphroditism of the lateral type is presented in which a cystic atrophic ovary was found in the left adnexa, a normal left Fallopian tube, a small uterus, and an atrophic testis in the right side of a bifid serotum.

2. Skin specimens from various portions of the body each revealed a male chromosomal pattern.

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JACKSONIAN SEIZURES IN INFANCY AND CHILDHOOD

JEAN HOLOWACH, M.D., DON L. THURSTON, M.D., AND JAMES O'LEARY, M.D.
ST. LOUIS, MO.

FROM 1934 to 1954 inclusive, 66 patients were admitted to the St. Louis Children's Hospital with the chief complaint of local motor or jacksonian convulsions. Another 48 with similar seizures were registered in the Pediatric Convulsive Clinic over a 5-year period from 1950 to 1955. A study of these 114 cases of jacksonian epilepsy in infants and children forms the substance of this paper.

Incidence.—The 48 out-patient cases were culled from a list of 637 consecutive cases of epilepsy of diverse types—an incidence of 1:13 or 7.5 per cent. The real frequency is probably higher. Generalized seizures not observed from the onset may have a focal origin (particularly true with nocturnal attacks) or local discharges may spread so quickly as to appear bilateral clinically. Patients reported to have generalized seizures, but with greater involvement on one side, were not included in this study.

Sex and Race Distribution.—In our series, 60 patients were boys and 54 were girls.

Only 1 (0.6 per cent) of the hospital patients and 10 (20.8 per cent) of the clinic group were Negroes. Since about 10 per cent of the hospital population and one half of our clinic patients are Negro, in both instances the ratio of Negro to white patients is far below average.

A study of the literature on racial distribution of epilepsy revealed contradictions and no unequivocal preponderance.

Age at Onset of Seizures.—Fig. 1 shows the age at onset of seizures. The range is from birth to 15 years with a maximum incidence in the first 2 years of life. Almost one half of the cases, 48 per cent, occurred before 3 years of age. Save for a secondary peak at 8 years of age, there is a progressive decrease in incidence from birth to adolescence. We believe this early onset of jacksonian seizures in children reflects etiological factors such as congenital cerebral defect, birth injury, and hereditary tendency.

No unusual association is apparent for the relatively high incidence at 8 years of age; 2 followed head injury, 1 was a patient with congenital hemiplegia, another gave a history of neonatal respiratory embarrassment, and 1 was a patient who several years previously had had encephalitis with neurological residuals; in the remaining 8 cases no etiology was manifest.

Of interest is the frequency of a long interval between cerebral involvement and the residual epilepsy. In 17 cases of hemiplegia evident within the first 2½ years of life, seizures on

From the Departments of Pediatrics and Neuropsychiatry, Washington University School of Medicine, and the St. Louis Children's Hospital, St. Louis, Mo.

the paretic side began after the age of 4½ years in 7 cases (respectively at 4½, 5, 5½, 6, 6, 8, and 11½ years of age). In a case of "spontaneous subarachnoid hemorrhage" at 3 months of age, jacksonian seizures began 4 years later. One patient developed recurrent jacksonian epilepsy 6 years after an apparent recovery from head injury associated with a depressed skull fracture. During the acute phase of the injury the child had had several jacksonian seizures.

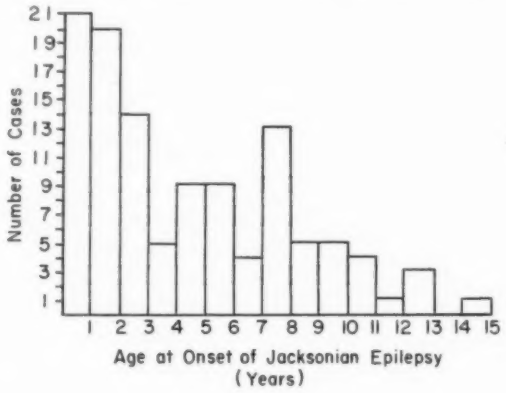

Fig. 1.

Walker[1] states, "The convulsions in posttraumatic epilepsy usually begin within 2 years of the cerebral injury; if a longer latent period exists, the possibility of some other etiological factor is enhanced." Our findings in the above and other instances demonstrate that a delayed onset of organic epilepsy is not exceptional in children. This confirms Penfield and Jasper's[2] impression of a delayed onset of posttraumatic epilepsy in childhood.

Family History of Epilepsy.—In 19 cases there was either no mention of a family history of epilepsy or it was unknown, uncertain, or distant. In the remaining 95 cases, the family history was positive in 27 cases (28 per cent). In one half of these, epilepsy was present in either the parents (10 cases) or siblings (4 cases). Seizures occurred in more than one member of the family in 4 cases.

Lennox[3] has reported the incidence of epilepsy among relatives of patients with organic seizures to be three times that of the general population. Other authors, Penfield and Jasper,[2] Ziskind and Ziskind[4] and, recently, Walker[1] have not been able to confirm this association. However, in a personal communication to Penfield and Erickson,[5] Lennox later stated that "when the symptomatic group of epilepsies is subdivided there is evidence of inheritance of the condition among those whose seizures begin early in life following trauma, while adult epilepties with brain tumors or traumata show no greater incidence of epileptic relatives than do a group of normal control persons." The extraordinary incidence of epilepsy in the close relatives of our young patients with jacksonian epilepsy confirms Lennox's observations.

ETIOLOGY OF JACKSONIAN SEIZURES

Jacksonian seizures imply local organic pathology. Nevertheless, a definite cause for the convulsions could be determined in only 39 cases or 34 per cent (Table I). The early age of onset of seizures suggests prenatal and paranatal factors as the most common cause of jacksonian epilepsy in childhood. The fact that 61 per cent of the cases with known etiology are on such a basis strengthens this impression. An uneventful delivery does not exclude birth injury. Keith and Norval[6] studied 57 infants with neurological lesions apparent during the first 2 weeks of life. Of 18 neonatal deaths, 6 had intracranial hemorrhage without history of a difficult delivery.

Birth Injury.—Thirteen patients (11 per cent) had a history of difficult delivery with neonatal asphyxia. Several others with prolonged or complicated deliveries were not included because of the lack of unequivocal signs or symptoms of brain damage in the baby.

TABLE I. JACKSONIAN SEIZURES

ETIOLOGY	NUMBER OF CASES
Birth injury	12
Birth injury plus ganglioneuroma	1
Infantile hemiplegia	11
Acquired CNS disease	11
? Acquired CNS disease	1
? Secondary to febrile seizures	1
Telangiectasis of cerebral cortex	2
Unknown	75

Type of delivery was mentioned in 9 of the 13 cases: one was by Caesarean section, 4 were spontaneous, 2 were vertex presentations with forceps application (one high), 1 was a footling breech with forceps, and another was a spontaneous breech with the umbilical cord wrapped around the neck. Four mothers in this group were eclamptic at the time of delivery—in 2, their infants were premature (1,830 grams and 2,310 grams). The smaller premature had congenital cataracts without mental retardation.

Two of the 13 patients (15.3 per cent) gave a family history of epilepsy.

Five of the group (38.4 per cent) had a hemiplegia detected before they had learned to walk.

Four patients had convulsions in the neonatal period. The nature of these was clear in only 1 case (jacksonian). Residual jacksonian seizures developed before 18 months of age in only 5 cases. In the remaining 8 patients, the age at onset ranged from 4 to 8 years. Seizures appeared after 6 years of age in 4 patients (30.7 per cent). As noted before, this delayed onset of epilepsy following brain injury in infancy differs from adult experience.

Infantile Hemiplegia.—Eleven patients without history of neonatal difficulty or subsequently acquired illness or injury had hemiplegias detected early in infancy (before 1 year of age in 6 cases and after 18 months in only one). One infant was premature (1,890 grams). There was a family history of epilepsy in 4 of these cases (36.3 per cent).

The age at onset of jacksonian seizures ranged from 6 months to 11½ years; 5 cases before 2½ years and 6, slightly more than 50 per cent, after 5½ years of age. Again we have evidence of delayed onset of residual epilepsy after cerebral injury.

Three patients had other convulsions prior to the onset of jacksonian epilepsy. Respectively, these were febrile, grand mal, and massive myoclonic seizures.

Acquired Disease of the Central Nervous System.—Eleven patients had postnatally acquired central nervous system disease.

Symptomatic skull fractures were responsible for 3 cases. Another head injury with a large open wound was included. Seizures occurred within 6 weeks of the accident. Since head injury is so common in children, in the above case, as in several others not included in this study, the head injury may have been coincidental. There was 1 case of encephalitis (type undetermined). Two cases were due to bacterial meningitis and 2 followed spontaneous subarachnoid hemorrhage. One patient had seizures on the basis of hypertensive encephalopathy of acute glomerulonephritis. The course of events in another patient—ruptured appendix, pelvic and abdominal abscesses, bacteremia, empyema, and then sudden onset of jacksonian seizures with hemiparesis suggested intracranial embolus or thrombosis.

Two other cases deserve comment. One had grand mal seizures during the course of malaria. Later she exhibited psychomotor and jacksonian seizures. Cerebral complications in malaria are recognized and may have been responsible for the seizures or they could be classified as simple febrile seizures. In the other case, illness was ushered in by generalized febrile convulsions and hemiparesis; coma persisted for 1 week. No systemic or central nervous system disease could be found. In infants and young children, very high fever associated with uncontrolled seizures has been known to cause brain damage.[7] Under such circumstances, one cannot exclude the possibility that subsequent seizures are a residual of such injury.

Excluding the above 2 cases, 8 of the 11 patients had hemiplegia evident at the onset of their injury or illness. This was transient in 3 and permanent in the remainder.

Two of the head injury cases had jacksonian seizures only during the acute stage of increased intracranial pressure. One of these developed temporal lobe epilepsy later. The patient with hemiparesis following a ruptured appendix had jacksonian seizures from the onset of illness. The remaining 8 patients developed or had recurrent jacksonian seizures from 4 weeks to 6 years after the primary disease (over 4 years in 3 cases). Occasionally other types of seizures occurred prior to the onset of jacksonian epilepsy. This was the case in the patients with meningitis and encephalitis.

Seven patients in this group (63.6 per cent) had more than one type of seizure. These were mostly of temporal lobe origin but grand mal with and without fever and myoclonic petit mal were also seen.

None of these patients with postnatally acquired brain disease gave a family history of epilepsy.

Space-taking Pathology.—Jacksonian seizures are invariably regarded with more concern than generalized convulsions. Of foremost concern is the possibility of a cerebral space-taking lesion. Considering the urgency of early diagnosis of brain tumor such an association may be warranted in adults but rarely so in infants and children. Intracranial tumor is seldom the cause of jacksonian epilepsy in the pediatric age group. In a series of over 800 children with focal discharging lesions of the brain studied by

Kellaway,[8] the incidence of neoplastic lesions was less than 2 per cent. We do not perform routine air encephalograms in cases of focal epilepsy in children unless there is evidence of increased intracranial pressure, neurological deficits or if the patient fails to respond to adequate anticonvulsant therapy. Livingston[9] also lists these indications for pneumoencephalography in patients with focal clinical seizures. Considering that such criteria may not present at the onset of focal seizures all of these patients must be examined at regular intervals to exclude a progressive organic lesion.

In the present series of 114 cases of jacksonian epilepsy, brain tumor was found in only one patient and was not necessarily related to the jacksonian seizures. This child sustained severe birth injury; ". . . the doctors thought they would never get him to cry and that he would die." From the age of one month to one year, he had daily jacksonian seizures. From 5 months to 3 years of age he also had daily akinetic or myoclonic seizures. Permanent hemiparesis was obvious early in life. Subsequent studies revealed a large ganglioneuroma in the region of the septum pellucidum and cortical sclerosis. It is tempting to consider the jacksonian seizures related to the atrophic cortical lesion and the akinetic seizures to the midline neoplastic lesion.

Diffuse surface hemangiomas were demonstrated in 2 cases. In 1, jacksonian seizures began at 4 months of age. There was right hemiparesis and mental retardation (IQ 41). At 6½ years of age she was referred here for study. X-rays revealed intracranial calcification in the left posterior parietal region. At surgery, a large venous hemangioma was found extending from the posterior part of the left parietal lobe to the Sylvian fissure and medially to the falx. In the other patient, jacksonian seizures began at 10½ years of age. Craniotomy revealed telangiectasis of the motor cortex paramedially.

CLINICAL ANALYSIS OF SEIZURES

About 20 per cent of the patients exhibited seizures of diverse types. This number does not include febrile convulsions, either generalized (6 cases) or focal (6 cases). Such evidence suggests diffuse rather than local brain dysfunction. Radiological and psychological findings support this impression. Five patients had grand mal epilepsy, 5 had myoclonic or akinetic seizures, 9 had classical temporal lobe seizures, and in 6 others the seizures are best described as "equivalents" (paroxysmal coma, headaches, abdominal pain). Four patients in the series had two or more different types of seizures besides their jacksonian ones.

Jacksonian Seizures.—Of the 114 cases of jacksonian epilepsy, 59 occurred on the right side and 51 on the left. In 3 instances, seizures occurred on either side on different occasions and in one case the parents were not certain which side was involved.

In only 60 cases was the exact site of origin mentioned. Most commonly the seizures started in the face (25 cases); 8 of these originated at the corner of the eye, 5 at the mouth. The remaining 12 were not localized further. Seventeen began in the "hand." The "arm" was mentioned as the primary site of involvement in

7 cases and the "shoulder" in 2. In only 9 cases did the seizures begin in the lower extremity; 6 in the "leg" and 3 in the "foot."

Thirty patients gave a history of abnormal sensation prior to movement in the part first involved. This was described as "pins and needles," "tingling," "numbness," "stinging," "warm" or "hot," "asleep" and "funny." Two patients experienced pain at the onset. Two had weakness or paralysis preceding the unilateral clonic convulsion. Four patients had visual auras—blindness, blurring of vision, or seeing colored lights. Frequently seizures consisted only of these sensory symptoms. Undoubtedly a higher percentage of patients had sensory aura than is reported here since this was not specifically asked for in the history. Furthermore, a good proportion of our patients were too young to express such feelings. Correctly speaking these are somatosensory or visual seizures with spread of neuronal discharge to the pre-Rolandic area.

Nocturnal jacksonian episodes are common. In the clinic group of 49 patients, 9 had jacksonian seizures only during sleep and in another case all seizures but one were nocturnal.

"Febrile" Seizures.—A considerable number of those having "febrile seizures" in infancy later have seizures without fever. These may be of any type. Six of our series had generalized seizures associated with fever prior to the onset of jacksonian epilepsy. In 4 of the 6, febrile seizures occurred on many occasions before the first jacksonian convulsion. In these cases one considers hereditary predisposition, undetected CNS disease at the time of the first febrile seizure, and the possibility of focal organic residual from the febrile episode itself.

In patients with febrile seizures there frequently is a high incidence of similar episodes in near relatives. Three of the 6 cases had a family history of convulsions, in 1 case the mother, in another the father, and in the third a first cousin.

In none of these 6 cases did the history suggest central nervous system disease responsible for the febrile seizures. Most often the febrile seizures were associated with respiratory infection and less frequently with gastrointestinal disturbances. In 1 case, the first seizure occurred at 19 months of age during an attack of "mumps." There was no clinical evidence of meningoencephalitis and subsequently this child had many febrile seizures before the onset of afebrile jacksonian seizures at age 3 years.

The age at onset of these "febrile seizures" was 5 months, 8 months, 10 months, 17 months, 3½ years, and 5 years, respectively. Except for the latter this age distribution is characteristic of febrile seizures.

In these 6 cases, jacksonian epilepsy appeared 6 months, 2 years, 2½ years, 3½ years, 8 years, and 12½ years individually after the febrile episodes. In one instance even the jacksonian seizures first occurred with fever. In the others the jacksonian seizures were afebrile. Subsequent to febrile convulsions in infancy, one patient later had repeated grand mal seizures without fever for several years before the onset of jacksonian epilepsy.

Electroencephalograms taken in every instance after the onset of jacksonian seizures were focal in 3 of the

6 cases. Two showed slow dysrhythmias and another had a paroxysmal nonfocal record.

Only 1 of these patients was mentally retarded. The mother had eclampsia at the time of delivery and there was severe neonatal asphyxia. Several febrile seizures associated with upper respiratory infections occurred at 3½ years of age. The jacksonian seizures began at age 6.

In 2 cases discussed in the section on etiology, we could not exclude the possibility that the first febrile seizure was on a basis of disease of the central nervous system. For this reason these are not included here.

Febrile Jacksonian Seizures.—Six patients had their first jacksonian seizure during an acute febrile illness or infection without fever (one case). Again these usually were uncomplicated upper respiratory infections and occasionally gastrointestinal.

Brain damage, evident for months or years before the onset of seizures in 3 of these cases supports our contention that fever and infection act as a trigger mechanism in precipitating latent jacksonian epilepsy. One of these children had meningitis in the first week of life. Subsequently she showed microcephaly with motor and mental retardation. At 16 months she developed jacksonian seizures. At first these occurred only with fever. Another patient with congenital left hemiparesis developed left jacksonian seizures at 2½ years of age. These were seen only with fever for several years before they occurred spontaneously. The third patient had a history of a difficult instrumental delivery and neonatal anoxia. Hemiparesis was detected in infancy. Frequent afebrile jacksonian seizures began at the age of one month. Later he had both generalized and unilateral seizures associated with febrile illness.

On follow-up, 5 of the 6 patients later had nonfebrile jacksonian seizures or continued to have both febrile and afebrile local seizures off and on for years.

To emphasize this relationship between fever and seizures, other observations deserve mention. One patient whose early seizures were jacksonian without fever later had such seizures precipitated by febrile illness. Two patients subject to both febrile and nonfebrile unilateral seizures had on different occasions generalized "febrile seizures." It appears that not only can patients with simple febrile seizures later have jacksonian seizures without fever but also that fever and/or infection can precipitate a latent trend for jacksonian epilepsy. The situation is analogous to the adult with grand mal epilepsy who, during childhood, had such seizures only with fever. Furthermore, patients with jacksonian epilepsy may exhibit generalized seizures at the time of febrile illness.

In sharp contract with the group who had generalized convulsions associated with fever prior to the onset of jacksonian epilepsy none gave a history of familial epilepsy.

Electroencephalograms were focal in 5 cases; 3 were paroxysmal focal and 2 showed a slow focal pattern. The sixth showed a nonfocal paroxysmal slow dysrhythmia.

Grand Mal Seizures.—In 37 cases the jacksonian seizures spread to the other side in a generalized convulsion on one or more occasions.

Five patients were reported to have had primary grand mal seizures. In 3 infants, the jacksonian seizures followed several months of generalized seizures. It is possible that in these cases a focal origin may have been unobserved. However, in at least 2 cases, it appears that bilateral seizures preceded the onset of jacksonian epilepsy. One child with congenital hemiparesis had many grand mal seizures from age 11 months to 6 years. At this time he developed focal seizures on the paretic side. The other child had a febrile seizure when 17 months old. At 20 months of age, she had her first afebrile seizure. From then until age 4 years she had repeated grand mal seizures without fever. At 5 years of age she first began having frequent jacksonian seizures.

Petit Mal Variants.—Only the clinical impression of atypical petit mal attacks is implied; the electroencephalograms did not necessarily conform with what is called *petit mal variant.*

Five patients had "atypical" petit mal of the akinetic or massive myoclonic type. Clinically, it is difficult to distinguish the two seizures. Since the distinction is questioned,[10] we have grouped the two together. No patient exhibited classical petit mal (simple staring).

Age at onset of these seizures in the 5 patients was 5 months, 17 months, 18 months, 2½ years, and 4½ years, individually.

None had a family history of epilepsy.

In only 1 case did the jacksonian seizures precede the atypical petit mal and it is possible that they were unrelated in etiology. This infant had a history of severe neonatal anoxia with congenital right hemiparesis and right jacksonian seizures since the age of 1 month. At 5 months of age he developed akinetic seizures ("slumping spells"). Surgical exploration revealed temporal lobe sclerosis and a large central ganglioneuroma. In the other 4 cases, jacksonian seizures occurred 1 month, 6 months, 2½ years, and 3½ years after the onset of the petit mal-like seizures.

There was clinical evidence of organic brain involvement in every case. One had severe microcephaly and another congenital hemiparesis. One patient developed akinetic petit mal 3 months following an illness with severe febrile seizures, prolonged coma, and hemiparesis. The fifth patient had encephalitis at 2½ years of age, with residual hemiparesis and mental retardation. At age 4½ years she began to have masticatory seizures and myoclonic spasms. At age 8 years, 5½ years after the original illness, she developed repeated jacksonian seizures.

Three of these 5 patients were grossly retarded, 1 questionably so and not determined in the other.

Other Seizures.—Nine patients had seizures suggesting temporal lobe origin—vertiginous aura, mastication, hyperacusis, manifestations of terror, and hallucinations. Frequently these were more disabling or caused greater concern than the jacksonian seizures.

Three patients had "syncopal epilepsy"—attacks of coma preceded by vague aura and followed by postictal phenomena (drowsiness, vomiting, headache).

Two had "cephalic epilepsy"—paroxysmal headaches suggestive of epileptic discharge.

One patient suffered recurrent attacks of abdominal pain consistent with the diagnosis of "abdominal epilepsy."

HEMIPLEGIA

Congenital and Acquired Hemiplegia.—Twenty-seven of the 114 patients (23.6 per cent) had hemiplegia. In 3 cases, due respectively to meningitis, hypertensive encephalopathy, and skull fracture, the hemiparesis improved. In the others it was permanent.

Etiology is listed in Table II. Fifty-nine per cent were congenital or due to birth injury.

Reference to a family history of epilepsy was made in 24 of the 27 cases. It was positive in 4. This incidence is only one half of that for the entire series.

TABLE II. HEMIPLEGIA (27 CASES)

ETIOLOGY	NUMBER OF CASES
Birth injury	5
Congenital	11
Hemangioma	1
Meningitis	2
Subarachnoid hemorrhage	1
Encephalitis	1
Embolus or thrombosis	1
Hypertension	1
Malaria	1
Fever of unknown origin	1
Head injury	2

Pneumoencephalography was performed in 13 cases. Abnormal findings were found in 10 (76 per cent).

Thirteen, or 48 per cent, of these patients showed degrees of mental retardation.

Postepileptic Hemiplegia.—Following local motor seizures, transitory paralysis is usual. Bravais[11] first described this phenomena in his thesis "l'epilepsie hemiplegique." Todd and Robertson[11] are credited for the hypothesis that this paralysis depends on temporary ganglionic exhaustion consequent to excessive discharge during the paroxysm. Apparently Hughlings Jackson[11] had independently arrived at a similar conclusion. Excluding the 27 cases of congenital or acquired organic hemiplegias, 40 of the remaining 87 patients in the series had a history of postictal paralysis of varied duration. The true incidence is undoubtedly higher. Minimal weakness may easily go unnoticed in an infant or young child and too often this information was not ascertained.

Jackson[11] states, "Nerve fibres being only exhausted, and not destroyed, as in some other kinds of paralysis, post-epileptiform paralysis is temporary, unless, of course, the fit recurs soon." Of particular interest to us were several patients in whom such paralysis became permanent. From 16 cases of permanent postictal paralysis, 10 have been selected. In the remaining 6, the follow-up period was too short or the circumstances such that other etiology was possible although unlikely. In all of the cases there was no apparent etiology; seizures occurring in healthy children without fever, dehydration, or other signs and symptoms.

Since recovery can occur over a period of weeks or months, prolonged observation is necessary before one can conclude that paralysis is permanent. All of the cases were followed for at least 1 year after the onset of a seemingly permanent residual; 5 have been followed from 5 to 21 years.

Seven of the 10 patients were 3 years of age or younger when their seizures began. This is probably significant. The immature brain is

believed more liable to extended postictal depression and to brain damage from repeated or prolonged seizures.

Residual weakness became apparent from as early as a few hours to as late as 7 years after onset of seizures. In the latter case a change of handedness several years before suggests an earlier onset of permanent paresis. With each seizure the duration of the Todd's paresis was variable but with a progressive degree of permanent disability.

In every case the attacks were of extreme frequency or prolonged duration or both. In 4, the jacksonian seizures occurred from one to hundreds daily and for a period ranging from 5 to 12 years in 3 of these 4. Two patients averaged seizures at least once a week for 2½ and 12 years, respectively. Seizures occurred at least once a month for 1 year in 1 patient and for 11 years in another. Frequent seizures were generally of short duration (less than one minute).

Four patients in this group showed abnormalities by ventriculography. Case 10 had been virtually in a state of "epilepsia partialis continua" for over 1 year, yet ventriculograms and arteriograms were normal. In Case 6, death from unrelated causes permitted examination of the brain. The left cerebral hemisphere was larger than the right with prominent sulci. There was moderate dilatation of the left lateral ventricle. Microscopic studies revealed no right-left difference in the cerebral cortex.

At the time of the last observation 9 patients were still having recurrent seizures.

Penfield and Jasper[2] cite several examples of postictal paralysis progressing in severity with each attack and with advancing cortical destruction. In addition to the metabolic disturbances concomitant with epileptic discharge, they considered the vascular changes observed during and after discharge of the exposed epileptic cortex as significant in the production of such paralysis.

The frequency of occurrence of progressive increase in the degree and duration of motor paralysis following jacksonian seizures, particularly in children, points clearly to the need for prompt recognition and treatment.

MENTAL RETARDATION

Evidence of mental deficiency was present *prior* to the onset of jacksonian seizures in 28 cases (24 per cent). Considering the nature and circumstances of these seizures, this incidence is not high. In the follow-up survey, 4 others were reported to have developed mental retardation consequent to recurrent convulsions. Serious behavior disorders were exhibited by 4—1 of these is included in the group with acquired mental retardation.

Twelve of these 28 cases had psychometric evaluation. Seven had IQ's of less than 50. In the remaining cases, mental retardation was apparent from the history and by examination.

Organic etiology or neurological abnormality was present in 19 of these 28 cases (67 per cent). These are listed in Table III.

Despite the severity of the neonatal distress only 7 of the 13 patients with recognized birth injury showed mental deficiency. The degree of retardation was questionable, mild or moderate in 6 cases and severe in only one.

Only 4 of the 11 patients with "congenital" infantile hemiplegia exhibited mental retardation.

Residual mental and motor retardation was seen in 3 cases following infections of the central nervous system (viral, bacterial, and parasitic).

Other recognized causes for mental defect were head injury in 1 case and diffuse cerebral hemangioma in another. Three patients had microcephalus or hydrocephalus of undetermined cause.

The high incidence of other types of seizures in these patients suggests diffuse brain damage. Twelve had "atypical" petit mal, grand mal, focal and generalized febrile convulsions or temporal lobe seizures, as well as jacksonian epilepsy.

TABLE III. MENTAL RETARDATION

ETIOLOGY	NUMBER OF CASES
Birth injury	7 (3 with hemiplegia)
CNS infection (viral, bacterial, parasitic)	3
Head injury	1
Hemangioma	1
Microcephaly	1
Congenital hemiplegia	4
Hydrocephalus	2
Unknown	9

Air encephalography was performed in 15 cases. Ten, 66 per cent, showed gross abnormalities; 5 were considered normal. One patient with a normal verticulogram demonstrated a large superficial venous hemangioma by arteriography.

Three of the 4 patients with acquired retardation had pneumoencephalograms with abnormalities seen in only one.

The 4 patients with serious behavior disorders had neither known cause for the seizures nor neurological deficits. Pneumoencephalography was performed in 1 case with normal findings.

THE ELECTROENCEPHALOGRAM

Properly used, the term *jacksonian seizure* connotes a discrete origin of convulsive discharge in the surface cortex of the opposite central region of the brain, the discharge spreading from the point of origin to become generalized. Using the plan of cerebral localization, the site of origin of a focal seizure can be inferred from the history, the signal symptom (that part where the first contraction or sensation occurs) being the important localizing event. If that signal symptom relates to the foot, the hand, or the corner of the mouth or eye, a further localization along the central gyri is permissible. Thus, face, hand, and foot signals implicate, respectively, the opposite Sylvian, intermediate and vertex parts of the central gyri.

Brain wave tracings are ordinarily obtained in free periods between seizures, and the following impressions are important in considering the data to be presented. With optimal electroencephalogram recording, it is ordinarily possible to detect even a quite circumscribed epileptogenic lesion and prove its position later by electrocorticography at operation. However, particularly in children, the scalp recording of a unique focal transient during an interseizure period may only signify an underlying focus of high excitability within a much larger area of disturbed functioning. Such a focus might be indistinguishable from one which relates to a discrete underlying epileptogenic lesion. Thus,

only by correlating the electroencephalogram findings with other neurological lateralizing signs, and with evidence from pneumoencephalography and arteriography, can we impute a site of structural disorder to a particular focal pattern. A focal spike, then, points only to the epicentre of a convulsive disturbance, and this discrete area of highest excitability may be presumed to trigger both the signal symptom of the clinical seizure and the spikes which are recorded during seizure-free intervals. Our experience with follow-up air studies in such cases, and less often with arteriograms, leads us to believe that the focal spikes which signify only a pathophysiological process significantly outnumber those in which a structural lesion can be imputed by other procedures as well.

Other impressions also aid in evaluating the findings in the present study. In serial tracings, each obtained in a seizure-free interval, a spike focus may be present on one occasion, absent on another. Thus, in dealing with a doubtful history of jacksonian seizures a single negative tracing will not rule out a focal origin for the convulsive process. Again, separate spike foci may appear in some cases, one related to each hemisphere. Both are not necessarily evident in the same tracing, and this may account for the instances in which a single record suggests the neurological paradox of a spike focus over the hemisphere ipsilateral to the seizure's initial manifestation. Generalized spiking can also occur in interseizure tracings from cases classified on clinical grounds as jacksonian. Even so, the repetitive spike discharge which develops at the onset of a clinical seizure in such a case differs qualitatively as well as quantitatively from the sporadic single spikes of generalized distribution recorded during interseizure intervals. Thus, the seizure discharge itself may have a discrete origin even though interseizure spiking is generalized.

There are also cases of jacksonian seizure in which spikes do not occur in interseizure periods, slow foci appearing instead. Compared with spike foci, slow focal patterns are more likely to relate closely to the suspected site of origin, and if they occur invariably at the same site in serial tracings are clearly suspicious of an underlying structural lesion. Again, only a generalized disturbance of rhythm, usually slow, may characterize the tracing in a jacksonian case, or the frequency of the interseizure tracing may even be quite normal. These variants are mentioned because even in the absence of interseizure evidence of a focus a convulsive tendency may still express itself at intervals.

The wide range of normal variability in the infant's electroencephalogram and the difficulty in securing artifact-free records makes the interpretation of focal changes more difficult than in older children and adults. In neonatal life, the subcortical centers mature more rapidly than does the cerebral cortex, and it is the electrical activity of the later maturing cortex which is expressed primarily in the electroencephalogram. Experimental evidence also indicates that it is more difficult for the immature cortex to synchronize a spike discharge. Even considering these difficulties, focal spikes can sometimes be recorded surprisingly early in neonatal life (6 days in our

experience); but in infants negative evidence has much less significance than in older children. Thus, if there is a strong suspicion of a focal convulsive process it is wise to repeat the tracing at intervals.

Prolonged postictal slowing of the young child's electroencephalogram is another factor which complicates the interpretation of the supposed jacksonian seizure tracing. A record made a few hours after either a focal or a generalized seizure may show markedly slow activity, and even asymmetry in amplitude between the traces from the two hemispheres to suggest a focal process. The same child, recorded during a seizure-free interval, may show a tracing which is much better ordered. Thus, it is advisable to repeat all tracings done in the postictal period to appraise the interval character of the electroencephalogram.

In evaluating the electroencephalogram of the present series of cases, the interval frequency pattern was classified: (1) as within the limits of variability of the normal for that age; (2) as mildly slow representing an equivocal departure from the normal; (3) as intermediate slow; and (4) as markedly slow. In occasional tracings, fast activity was intermingled with intermediate or markedly slow activity; these were classified as mixed fast and slow. Convulsoid transients were considered apart from the resting frequency, all highly synchronized transients of unique form being classified as spikes. Finally, slow patterns which appeared consistently at one lead were classified as slow foci.

Of 83 children in the series who had electroencephalograms, 18 had neurological lateralizing signs leading to the presumption that structural abnormality involved a part or all of one hemisphere. Of that 18, only 3 (from the out-patient series) showed resting frequencies that could be considered normal, and all of them showed focal or generalized intermittent spiking. In all other tracings from this group, the resting frequency showed intermediate or markedly slow departure from the normal. Of the 18 cases, 10 presented focal spiking over the central region of the suspected hemisphere, and in 3 others spikes of generalized distribution were recorded. In only 1, was the focal spike process recorded from the nonsuspect hemisphere. There were also 2 slow wave foci detected over the central region of the suspected hemisphere. The remaining 2 showed only an intermediate or markedly slow disorder of the usual resting rhythm. Thus, in 12 of the 18 cases a focal process was recorded in the expected locale.

Of the 65 cases without evidence of neurological abnormality, 17 or one fourth showed a normal resting frequency. Of the 17, 5 showed focal spikes at the suspected site and 6 generalized or at least nonfocal spiking. The resting frequency of the remainder was classified as intermediate or markedly slow. Of the total cases without neurological abnormality, 19 showed focal spike processes where it was suspected that they might occur, but in 6 others the focus was paradoxical, appearing over the nonsuspect hemisphere. In one of the latter group, ventriculograms were done and proved to be normal. There were also 15 cases which showed generalized spiking. Slow focal patterns were recorded in 7 of the group and all occurred over the central region of the

suspected hemisphere. Of the remainder, 1 showed a completely normal tracing and the others only intermediate or markedly slow resting frequencies without focalization.

The chronological span was 5½ months to 14 years. Disregarding coincident neurological abnormality for the moment and rating only on the basis of success in recording a focal process of 12 children under 2 years of age, 5 had spike foci over the suspected hemisphere and in 5 others the localization was equivocal, nonfocal, or paradoxical; 2 showed no spikes at all. Compared with the cases over 2 years, the expectancy for obtaining a consistent localization was significantly lower.

We conclude that the expectancy for recording a focal pattern over the suspected hemisphere in a jacksonian seizure case increases with age and also with the coexistence of other evidence of neurological abnormality. However, focal processes are not of themselves pathognomonic of an epileptogenic lesion, for our results indicate that the number of cases with focal disorder in which no other neurological abnormality could be found was significantly larger than the group in which a neurological abnormality could be proved to coexist.

AIR ENCEPHALOGRAMS

Adequate air encephalograms by the spinal subarachnoid route or by ventricular punctures were made in 47 cases. Only one half were considered abnormal.

Six of the 13 cases with recognized birth injury had air studies. Abnormalities were demonstrated in all but one. Two had moderate bilateral symmetrical ventricular dilatation. One showed atrophy of the right cranium with dilatation of the corresponding ventricle. In another there was unilateral ventricular dilatation with a mild degree of porencephaly, cysts communicating with the anterior part of the body and anterior horn of the lateral ventricle. The fifth case had suprasellar calcification. At ventriculography, a calcified tumor was seen in the left lateral ventricle infiltrating the septum and pushing it to the right. At surgery this patient had two lesions—cortical sclerosis in the side opposite the hemiplegia and a benign ganglioneuroma attached to the septum pellucidum and extending into the lateral ventricle.

Pneumoencephalography was performed in 7 of the 11 patients with congenital hemiplegia. Five showed abnormalities. Two had relatively localized lesions, 1 a minimal cortical atrophy of the left frontoparietal region (right hemiplegia) and the other a porencephaly in the left frontoparietal region (right hemiplegia). In 2 cases, there was a unilateral dilatation of the ventricular system with a shift to the side opposite the hemiplegia. One patient showed bilateral cortical atrophy, greater on the side opposite the hemiplegia.

Only 3 of the 13 patients with postnatally acquired central nervous system disease had air studies. Clinically, each exhibited hemiparesis and pneumoencephalograms revealed contralateral ventricular dilatation.

In the remaining 11 cases with abnormal pneumoencephalographic findings, no etiology was apparent. Six had symmetrical dilatation and in the remainder there was unilateral ventricular dilatation.

Ten of the 24 patients with gross pneumoencephalographic abnormalities were retarded mentally by clinical or psychometric evaluation. Another who early exhibited only a severe personality defect, when seen 6 years later, during which time he continued to have seizures, appeared unquestionably mentally retarded.

Since space-taking lesions, neoplastic or otherwise, are rarely the cause of jacksonian seizures in infants and children it has been our policy to postpone air encephalography unless there is evidence of increased intracranial pressure, neurological deficit, or a failure of response to adequate anticonvulsive therapy.

In the infant, subdural taps are recommended to exclude subdural hematoma. These are more essential than air studies. We have seen several cases of large bilateral subdural hematoma in which pneumoencephalograms were normal. On the other hand, angiography, when correctly performed, will rule out a subdural hematoma.

Cerebral arteriograms were made in 6 cases with abnormal findings in only 1. Two of the 5 patients with negative arteriograms showed abnormalities by pneumoencephalography. On the other hand, the 1 patient who showed abnormal arteriograms had normal ventriculograms.

SUMMARY

One-hundred and fourteen cases of jacksonian epilepsy in infants and children are reviewed.

Incidence.—The reported frequency of local motor seizures, 7.5 per cent is probably too low because of failure of observation from onset or rapid spread of epileptic discharge.

Sex.—Both sexes were about equally affected.

Race.—The ratio of Negro to white patients was considerably below the hospital average.

Age At Onset.—The greatest incidence was among infants and young children with a progressive decline toward adolescense. Forty-eight per cent were less then 3 years of age. It seems logical to implicate pre-, peri-, and postnatal factors in etiology.

A delayed onset of organic epilepsy was usual.

Heredity.—Twenty-eight per cent of 95 cases had a history of epilepsy in close relatives (half in parents or siblings). This confirms Lennox's impression of the influence of heredity in organic epilepsy in children.

Etiology.—Cause was known in only 34 per cent of cases. Almost two thirds were related to birth injury (13 cases) or congenital or infantile hemiplegia (11 cases). Eleven patients had postnatal acquired disease of the central nervous system of varied etiology. Diffuse surface hemangiomata were demonstrated in 2 cases. Only one patient had an expanding intracranial lesion. The latter also had severe birth injury with hemiplegia and extensive cortical sclerosis. Cerebral neoplasm is a relatively rare cause of jacksonian epilepsy in infants and children.

Seizure Analysis.—There was no right or left predominance of jacksonian phenomena. One third had bilateral spread. The commonest site of origin was the face or hand. Only 9 of 60 cases began in the leg. Abnormal sensation prior to movement was common. Nocturnal attacks were fairly frequent.

Six patients had febrile seizures before the onset of jacksonian epilepsy. In 4 these were of great frequency. The interval between the febrile and jacksonian seizures was over 2 years in 5 of the 6 cases. One half of this group had a family history of epilepsy. Occasionally, circumstances suggested that jacksonian epilepsy might be a residual of local brain damage from severe and protracted seizures with high fever.

In another 6 cases, early jacksonian seizures occurred only with fever and infection. The presence of severe neurological abnormalities prior to the onset of seizures in 3 of these cases confirms the impression that fever and infection can trigger a latent tendency for jacksonian epilepsy.

Twenty-five patients had other types of seizures. Five had grand mal epilepsy prior to the onset of local seizures. Five with organic brain involvement had "atypical" petit mal (myoclonic or akinetic). In 4, these preceded the onset of jacksonian epilepsy. Fifteen patients had recurrent paroxysmal phenomena compatible with epileptic discharge without motor component.

Hemiplegia.—Twenty-seven patients (23.6 per cent) had hemiplegia. The majority were attributable to prenatal factors or birth injury. Forty-eight per cent were mentally retarded. Post-epileptiform paralysis (Todd and Robertson) of varied duration was common. With frequently recurring or prolonged seizures such paralysis may be progressive and ultimately permanent. This was the case in at least 10 patients in our series. This course of events attests to the need for prompt control of jacksonian seizures.

Mental Retardation.—Twenty-eight patients (24 per cent) were mentally retarded prior to onset of jacksonian epilepsy. Etiological factors were evident in two thirds. Four patients appeared to develop mental retardation consequent to severe recurrent seizures. Serious behavior disorder was a chief complaint in 4 children.

The Electroencephalogram.—In general, the conformance of focal electroencephalogram findings with inferences drawn from pattern of seizure is good, even when only a single tracing is available. An expected electrographic focus is more likely to be demonstrated in a child than in an infant. Spike foci are nonspecific indicators of a region of high cortical excitability, and not necessarily of underlying structural abnormality. Slow wave foci, recorded with or without accompanying focal spike discharges, more frequently presage proof of underlying structural disorder.

Of the 83 children in the series who had electroencephalograms, 18 had neurological lateralizing signs. In 12 of these, a focal process was recorded in the expected locale. In the remaining 65 cases without neurological abnormality, 19 showed focal spike processes in the suspected hemisphere and in 6 others the focus was paradoxical. Fifteen showed generalized spiking. Seven showed slow focal patterns over the central region of the suspected hemisphere. One tracing was normal and the remainder showed intermediate or markedly slow resting frequencies without focalization.

Air Encephalograms.—Close observation of patients with local seizures is essential. Encephalography is not routine. Criteria for air studies are

increased intracranial pressure, neurological abnormalities or failure of response to adequate antiepileptic therapy. One half of the encephalograms made were considered abnormal. Recognized cause for these abnormalities was present in only 13 of 24 cases. Ten of the 24 patients with abnormal air studies were retarded mentally. Arteriograms were sometimes abnormal with normal pneumoencephalograms and vice versa.

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Accidental Deaths in Infancy

Infants found dead in bed, are not generally killed by being lain on by their mothers, but by being suffocated under the bed-clothes, with carbonic acid gas exhaled from their own lungs and re-inspired. They die without pain, in a profound sleep. Mothers, give your babes more air. Let them sleep with their heads uncovered. Do not let them go to sleep on or under your arm, for when you cover yourselves, in the half unconsciousness of partial sleep, you will cover your darlings' heads also, and in the morning may find them still in sleep—a sleep from which your caresses cannot awake them.

FROM THE PACIFIC MED. AND SURG. JOURNAL, 1858.

VOMITING IN INFANCY AND EARLY CHILDHOOD: TREATMENT WITH PROCHLORPERAZINE

C. E. HOPKINS, M.D., AND T. V. GEPPERT, M.D.
MADISON, WIS.

PROMPT treatment of physical disorders in children is often seriously impeded by the presence of persistent vomiting. Not only does vomiting interfere with the oral administration of medication at home, but it also, by dehydration, lowers the child's capacity to withstand physical disease. The need to check vomiting, therefore, may often become imperative.

In recent years the antiemetic activity of a number of phenothiazine derivatives has been studied.[1-3] Among the newest of these derivatives is prochlorperazine (Compazine*), which has been reportedly effective as an antiemetic in adults.[4, 5] The drug also functions as a tranquilizer.[6, 7]

Recently, prochlorperazine became available in syrup form for investigational use in pediatrics. The authors undertook to evaluate prochlorperazine for the efficacy of its antiemetic activity and its suitability for pediatric practice.

METHOD

The 44 children selected for this study ranged in age from 4 months to 9 years. All of them had suffered three or more vomiting episodes daily. Symptoms of one or more of the following conditions were present in 36 patients: acute gastroenteritis, measles, mumps encephalitis, diarrhea, acute pharyngitis, acute nasopharyngitis, pertussis, acute glomerular nephritis, acute tonsillitis, streptococcal pharyngitis, and atherostomatis. Vomiting had persisted, sporadically, from 18 hours to 3 days prior to treatment with prochlorperazine. In the other eight patients, in addition to vomiting, one or more of the following symptoms were seen: nervousness, overactivity, insomnia, abdominal pain of unknown origin, eye blinking, and facial grimacing. These eight patients had been vomiting sporadically for 7 to 10 days before treatment began. The patient with abdominal pain showed no evidence of intestinal obstruction or other pathological conditions.

Doses were graduated from 2.5 mg. (or ½ teaspoonful) three times a day for the youngest patients, to 5 mg. four times a day for the oldest patients. Concomitant with the administration of the antiemetic, therapy directed to the underlying condition was given to 18 patients. This concomitant therapy included diet restriction, antibiotics in cases with bacterial infection, and intravenous fluids for dehydration. There was no concomitant therapy for any of the psychically disturbed patients.

In evaluating the efficacy of the drug, promptness of antiemetic action

From the Dean Clinic and the Pediatric Department, University of Wisconsin Medical School.

*Smith Kline & French Laboratories.

was considered of prime importance. A patient whose vomiting abated after the first or second dose was considered to have made an excellent response. Abatement of vomiting within twelve hours, or a single, mild vomiting episode following an excellent response, was rated good. A reduction in the number of episodes of vomiting was rated fair. Anything else was considered poor. Abatement of vomiting was considered achieved when oral fluids and medication were retained. Naturally, other factors—side effects and acceptability of the medication to the patients—were also considered in evaluating the responses.

RESULTS

Of the 36 patients whose vomiting was associated with organic disease, 14 had an excellent response, vomiting abating after the second dose in almost every case. A good response was seen in 19 patients, a fair response in 1 patient; 2 patients showed no appreciable improvement. Thus, 92 per cent of these young patients were free of vomiting—and were able to retain fluids and medication—within a twelve-hour period; that is, after three or, in a few cases, four doses.

Those patients whose vomiting had persisted for less than 36 hours before onset of medication had a higher percentage of excellent responses than those patients whose vomiting had persisted for more than 36 hours. The medication seemed to be as effective in the infants as in the older children. Of the 8 children in the study who were less than 1 year old, 7 were free of vomiting within twelve hours. Of the 8 patients whose vomiting was associated with psychic disturbance, 3 had a good response to prochlorperazine, 1 a fair response, and 4 did not show any appreciable improvement.

In neither group of patients were there any observable side effects. No patient manifested jaundice, abnormal urinary findings, or change in white or red count. The patients' parents reported, in most cases, that the fruit-flavored syrup was acceptable to the children, and that resistance to second and third doses was either less than to initial doses or was absent entirely.

DISCUSSION

Although the group of patients is relatively small, we were pleasantly surprised by the fact that 92 per cent of these patients showed a marked improvement in vomiting in 12 hours or less. Since antibiotics frequently induce vomiting, prochlorperazine faced a particularly significant test in 7 children who received concomitant antibiotic therapy. Yet, 5 of these patients were free of vomiting within 6 hours, and all 7 were relieved of vomiting within twelve hours.

Although half of the psychically disturbed children responded favorably to the antiemetic, it must be borne in mind that psychic disorders frequently require extensive and prolonged treatment. It is of interest, however, that the use of prochlorperazine as an antiemetic in these psychically disturbed children was in no case attended by the side effects frequently associated with certain other antiemetic therapies. Our past experience with barbiturates in the treatment of emotionally induced vomiting, for example, is similar to Gatski's,[8] who found that barbiturates

tend to make disturbed children inaccessible even to superficial psychotherapy and, in some cases, actually excite the child further.

Although there were no observable side effects, it must be kept in mind that many of these very young patients are quite inarticulate and are therefore unable to communicate their subjective reactions clearly. Nevertheless, the writers received the distinct impression that prochlorperazine caused little, if any, discomfort and distress among the children in the study. The patients seemed quieter, though not sedated, and less apprehensive of pain. Whether these desirable effects were due to the tranquilizing action of prochlorperazine and/or the drug's prompt antiemetic activity is difficult to tell.

Since antiemetic drugs may mask acute surgical conditions, they must be used cautiously in pediatric practice, and only after examination and diagnoses have excluded such conditions as appendicitis. This caution is particularly apt in respect to prochlorperazine because of its effectiveness and promptness in controlling vomiting.

Prochlorperazine demonstrated low dosage requirements. Its administration was safe and uneventful when given to patients as young as 4 months of age.

SUMMARY

Prochlorperazine was given as an antiemetic to 36 young children suffering from persistent vomiting associated with physical diseases, and to 8 children suffering from persistent vomiting associated with emotional disturbance.

Of the children whose vomiting accompanied physical disease, 92 per cent were relieved of vomiting within twelve hours after the initial dose of prochlorperazine or after a total of three doses. Of the children whose vomiting was associated with emotional disturbance, 50 per cent were relieved of vomiting episodes in the twelve-hour period. Prochlorperazine also seemed to exert a tranquilizing effect on the patients, for they seemed less restless and apprehensive. There were no observable side effects.

Prochlorperazine was found to be an effective and safe antiemetic for pediatric practice.

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TRANSPLACENTAL PASSAGE OF THE L. E. FACTOR

FRITS MIJER, CAPTAIN, MC, USAR, AND RALPH N. OLSEN, CAPTAIN, MC, USA
DENVER, COLO.

IN 1954, Bridge and Foley[1] demonstrated the L. E. cell in the cord blood and bone marrow of a newly born baby of a mother with disseminated lupus erythematosus. Brief mention was made of another mother with this disease, where again the L. E. cell was demonstrated in the cord blood of her offspring. The authors believed that placental transmission of the L. E. factor had occurred. In 1957, Berlyne, Short, and Vickers[2] reported two more mothers with disseminated lupus erythematosus who gave birth to babies in whose peripheral blood L. E. cells were seen. Transplacental passage of the L. E. factor was also thought to have occurred in these instances.

We wish to report a fifth case of probable placental transmission of the L. E. factor from mother to baby. In our case, the mother also had established disseminated lupus erythematosus and L. E. cells were repeatedly demonstrated in the peripheral blood of her baby.

CASE REPORT

The mother was a 22-year-old white girl who was in good health until the age of 15 years when she was found to have idiopathic thrombocytopenic purpura; a splenectomy was performed after which she had a complete recovery. She remained well until her first pregnancy at the age of 20 years. After three months' gestation she developed migratory arthralgia, recurrent fever, general malaise, and intermittent rash on the lower extremities. Repeated bone marrow and peripheral blood examinations demonstrated the L. E. phenomenon. She delivered a viable male infant after thirty-five weeks' gestation. The infant died within 24 hours. Clinical features and autopsy findings were consistent with the diagnosis of "hyaline membrane disease." The placenta was normal on gross and microscopic examination.

Two months after her first pregnancy the patient was started on cortisone, 100 mg., which she received for one year when it was changed to Meticorten, 25 mg. daily. The patient did very well and Meticorten was gradually decreased to 10 mg. daily.

The second pregnancy was uncomplicated. The patient remained on Meticorten throughout her pregnancy. After nine months' gestation, there was a normal low forceps delivery (Dec. 6, 1956). The placenta was normal on gross and microscopic examination. Laboratory studies done on the mother's blood on the day of delivery revealed a hemoglobin of 15.0 Gm. per 100 c.c. of blood; the hematocrit was 46 per cent; L. E. examination (non-clotted method) on the peripheral blood was positive; blood group A, Rh negative; serologic test for syphilis was negative. Urinalysis revealed 2+ albuminuria with occasional red blood cells per high-power field (centrifuged specimen). Post-partum course of the mother was uneventful.

The baby was a normal female. The weight was 6 pounds 1 ounce and the

From the Department Pediatrics, Fitzsimons Army Hospital, Denver 8, Colo.

length was nineteen inches. Blood group was A, Rh positive. The cord bilirubin was 0.3 mg. per cent direct and 3.0 mg. per cent indirect. The Coombs' test (direct and indirect) was negative. The hemoglobin was 20 Gm. per cent and the hematocrit 60 per cent. There were normoblasts, 1,800 per cubic millimeter. During the second day of life, the baby was reported to be dusky on several occasions; she vomited several times. At the age of 20 hours, an L. E. preparation was done on the peripheral blood of the baby (nonclotted method) and found to be positive (Fig. 1). During the third day of the baby's life she continued to vomit. The cord was noted to be foul smelling and was removed. Cultures of the blood and umbilical cord stump were obtained, and the patient was started on penicillin and streptomycin. Blood chemistries that day revealed sodium of 145 mEq. per liter, chloride of 107 mEq. per liter, and potassium of 5.9 mEq. per liter. The white blood cell count was 16,600 with 66 per cent neutrophils, 29 per cent lymphocytes, 3 per cent monocytes, and 2 per cent eosinophils. On the fourth day of life the child was noted to be jaundiced. Serum bilirubin (age 90 hours) revealed a total of 15 mg. per cent with an indirect value of 14.55 mg. per cent.

Subsequent specimens drawn at the age of 102 hours showed a serum bilirubin of 18.0 mg. per cent with an indirect value of 17.4 mg. per cent. Repeated L. E. preparations which were done daily during her hospitalizations were all found to be markedly positive. However, no rosette formation was noted. Electrophoretic protein pattern obtained at the age of 5 days revealed albumin, 4.221 Gm. per cent, and globulin: alpha I, 0.297 Gm. per cent; alpha II, 0.416 Gm. per cent; beta, 0.654 Gm. per cent; and gamma, 0.862 Gm. per cent. Serum complement determination done on the same blood specimen[3] showed a level of 9.5 U. 50 per cent (U. 50 per cent is used

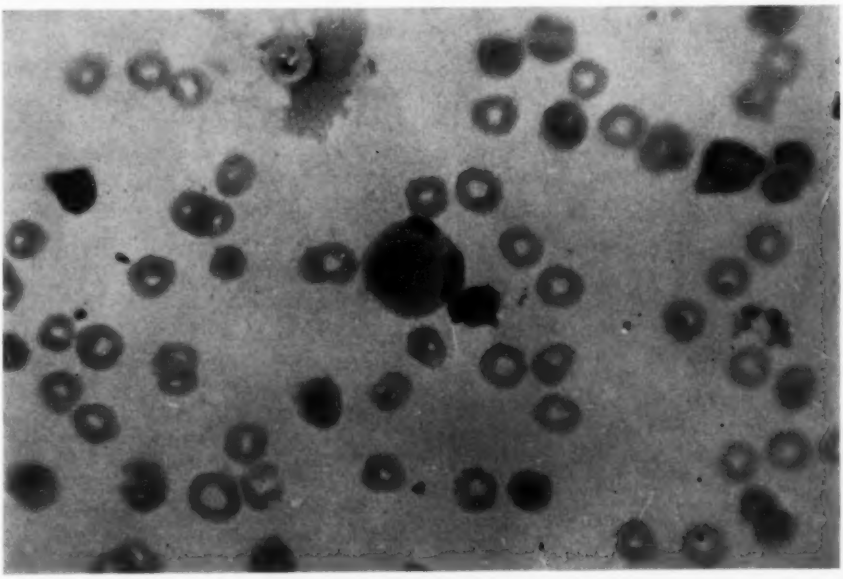

Fig. 1.—L. E. cell in infant's peripheral blood.

to indicate 50 per cent hemolytic units per milliliter of undiluted serum).

After the fifth day of life the child did very well. She stopped vomiting, and the jaundice disappeared. Blood culture and throat culture (obtained shortly after birth) showed no growth. Culture from the umbilical cord stump grew out *Staphylococcus aureus.* Chest roentgenograms taken on the third and fifth days of life were within normal limits. The baby was discharged eight days after birth in good condition.

During her hospitalization and subsequent to her discharge the baby was fed by bottle, since the mother did not have any breast milk.

The baby was followed in the Outpatient Department where repeated L. E. examinations were found to be positive on weekly examination up to the age of 7 weeks; however, during the last three weeks it had been very hard to find any L. E. cells and the ones which were noted were of poor quality. Three biweekly L. E. preparations after the seventh week were negative. No rosettes were seen at any time. The baby was last seen at the age of 8 months, at which time she showed excellent growth and development.

DISCUSSION

In the case described by Bridge and Foley and the cases described by Berlyne, Short, and Vickers, the L. E. cell could still be demonstrated in the peripheral blood of the baby at the age of 7 weeks but not beyond that age. In our case, similarly, the L. E. cell was not present after the age of 7 weeks.

The duration of the L. E. phenomenon corresponds roughly to the half-life of gamma globulin and appears to support the conclusion of passive transfer of the L. E. factor[1] (the L. E. factor being a component of the gamma globulin fraction as shown by Haserick[4]).

Glagov and Geehman[5] speculated upon the possible relationship of transplacental L. E. factor passage and the familial occurrence of disseminated lupus erythematosus. They suggested possible concomitant transplacental transmission of antigenic substances provoking antibody formation and eventually an anaphylactic sensitivity or, perhaps, the L. E. factor itself being transmitted and sensitizing the fetus to some unknown antigen.

If the presence of the L. E. factor in the offspring of a patient with disseminated lupus erythematosus during the newborn period is more than just passive transfer and perhaps a subclinical immunological manifestation, one might expect a depressed serum complement level.

The serum complement level at the age of 5 days was 9.5 U. 50 per cent (measurement of 50 per cent hemolytic units per milliliter of undiluted serum). Ten normal infants were tested, all at the age of 5 days, and found to have serum complement levels ranging from 8.58 to 33.90 U. 50 per cent (mean 17.43 U. 50 per cent).* Serum complement level in our patient at the age of 3 months was 18.0 U. 50 per cent and at 6 months was 33.5 U. 50 per cent. Very few data exist on serum complement levels during the newborn period; the levels which have been reported show a wide range.[6, 7] The serum complement level

*Method as described in Pediatrics 11: 570, 1953, by Janeway and Wedgwood, except that cell suspension was adjusted by method of Kent, Bukantz, and associates, using the formula $V_2 = \frac{V_1 O_1 D}{0.500}$.

of our patient, although low at the age of 5 days, appears to fall within the normal range. Conclusions from a single case would be premature. In this instance, however, there is no evidence to suggest a hypersensitivity phenomenon immediately after birth.

SUMMARY

A case of transplacental transmission of the L. E. factor is presented. Serum complement and gamma globulin levels in the offspring were within normal range.

We wish to thank Dr. Jack E. Githens, Associate Professor of Pediatrics, University of Colorado, for reading the manuscript and Master Specialist L. B. Nolte, USA Research and Development Unit, Fitzsimons Army Hospital, for technical assistance.

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Multiple Births

How Many Children Can a Woman Bear?—Dr. Szukits says that this question has not yet been satisfactorily answered. He himself has observed two females, each of whom had borne twenty-four children. Osiander (*Handb. d. Entbindungs Kunst*, 1 Theil, 1 Abth. S. 319) mentions one woman who during her married life bore 44 children, and another who had 53. Burdach (*die Physiol. als Erfahrungswissenschaft*, 1 Bd. 1826, S. 410) relates that the wife of a countryman in the Moscow district had given birth to 69 children at 27 confinements—four times four at one birth, seven times three, sixteen times twins. In the year 1809, the Vienna newspapers contained the following announcement: Maria Anna Helm, the wife of a poor linen weaver in Neulerchenfeld, 20 years married, bore at 11 confinements 32 children; 28 living, and 4 dead: 26 were males, and 6 females; all were begotten by one man, and nursed by herself.

Six children seem to be the largest number ever produced at one birth. A perfectly trustworthy instance of this is the following: The *Schwäb. Mercur*, 1805.—The wife of a chimney-sweep here, named "Döpfer," was yesterday confined of six children; all were boys, and dead. This woman, who has been twice married, has already given birth to 44 children. During her first marriage, which lasted twenty-two years, she bore 27 boys and 3 girls. In her second marriage, which has lasted but three years, she has born 14 children—3 at the first, 5 at the second, and now 6 at third confinement (Osiander, 320).

ED. MED. JOURN., JUNE, 1858, FROM ZEITSCHRIFT, d. K. K. GESELLSCHAFT D. AERZIE ZU WIEN, JULY AND AUGUST, 1857.

UNEXPLAINED DEATH FROM EXCHANGE TRANSFUSION

WILLIAM C. TAYLOR, M.B., CH.B., LLOYD C. GRISDALE, M.D., AND
ALLAN G. STEWART, PH.D.
EDMONTON, ALBERTA

DURING the 11 years that have elapsed since the introduction of exchange transfusion for the treatment of hemolytic disease of the newborn, attention has been periodically focused on the fact that this procedure is not without its dangers and may occasionally be associated with unexpected fatality. Allen and Diamond[1] have recently pointed out that, with few exceptions, it has been impossible to explain the deaths that arise during or shortly after exchange transfusion. Walker and Mollison[2] have listed the causes of death occurring in association with hemolytic disease of the newborn in England and Wales during the years 1953 and 1955. In 88 (16 per cent) of 550 deaths, the fatality arose during or within 4 hours of exchange transfusion. The immediate cause of death was not apparent in these cases but, from the clinical information available, it seemed that death should not otherwise have taken place at that time.

The following case reports are presented in the belief that they represent a sequence of events which must occur in a certain but at present unknown proportion of sudden deaths arising during exchange transfusion.

From the Department of Paediatrics, University of Alberta and University of Alberta Hospital, Edmonton, Alberta.

CASE REPORTS

CASE 1.—*Cardiac Arrest During Exchange Transfusion.*—

This female infant was delivered by cesarean section on the tenth of September, 1957. Cesarean section was performed at 35 weeks' gestation because of a rise in maternal D antibody titer to $\frac{1}{32}$, and because of the death of the 3 preceding siblings from hemolytic disease. The infant weighed 2,220 Gm. She cried spontaneously and on examination appeared normal except for yellow staining of the vernix and the umbilical cord. The spleen was not palpable. The cord blood serum bilirubin was 6.4 mg. per cent, hemoglobin 9.5 Gm. per cent, hematocrit 26 per cent, and reticulocyte count 14.4 per cent. The direct Coombs' test was positive.

The first exchange transfusion was carried out within one hour of delivery. Using a 10 c.c. syringe, 415 c.c. of blood were withdrawn and 384 c.c. of packed cells injected. Throughout the 1-hour procedure the infant's condition remained satisfactory. Following the exchange, the serum bilirubin was 2.5 mg. per cent, the hemoglobin 13.4 Gm. per cent, and the hematocrit 35 per cent.

At the age of 7 hours, the serum bilirubin had risen to 9.0 mg. per cent and a second exchange transfusion was given. Using the same technique as before, 310 c.c. of blood were withdrawn and 290 c.c. injected in less than 1 hour. The infant's condition remained satisfactory throughout and periodic electrocardiographic (ECG) tracings taken with a direct writing

Sanborn electrocardiograph revealed no abnormalities in the standard leads. A few minutes after the exchange had been completed the infant developed a generalized convulsion which responded to intramuscular injection of 2 c.c. calcium glucoheptonate. During the next few hours, a few petechial hemorrhages developed on the skin of the face and trunk.

At the age of 22 hours, the serum bilirubin was 13.6 mg. per cent, the hemoglobin 8.3 Gm. per cent, and the hematocrit 21 per cent. A third exchange was attempted using 7-day-old blood which had been packed by removal of supernatant plasma a few hours before the exchange. After 80 c.c. of blood had been withdrawn and 70 c.c. injected, an ECG tracing taken

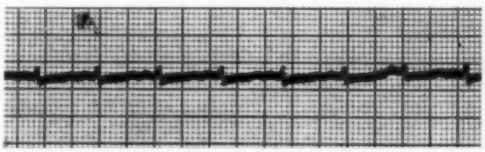

Fig. 1.—Case 1. Lead I. Time from start of exchange—17 min.; volume of blood injected—30 c.c.; normal nodal rhythm, rate—135 per minute.

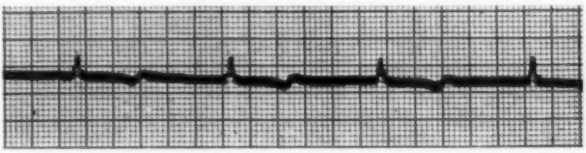

Fig. 2.—Case 1. Lead I. Time from start of exchange—28 min.; volume of blood injected—70 c.c.; slow nodal rhythm, rate—53 per minute.

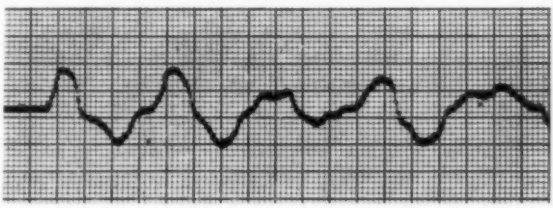

Fig. 3.—Case 1. Lead I. Time from start to exchange—30½ min. Ventricular fibrillation.

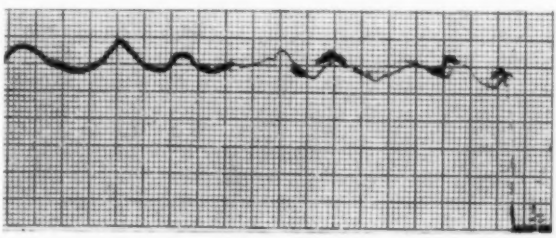

Fig. 4.—Case 1. Lead I. Time from start of exchange—32 min. Cardiac arrest.

28 minutes after the commencement of the exchange showed evidence of slow nodal rhythm. (Figs. 1, 2, 3, and 4.) During the next 4 minutes, the cardiac slowing progressed to ventricular fibrillation and complete cardiac arrest. At the time of detection of the cardiac slowing the infant's condition appeared satisfactory. There were no signs of respiratory distress, cyanosis, or pulmonary adventitious sounds. Clinical signs of collapse were only apparent when the ECG tracing showed evidence of ventricular fibrillation. The cardiac arrhythmia was uninfluenced by discontinuing the exchange and immediate injection of 2 c.c. calcium glucoheptonate into the umbilical vein. The heart remained in asystole for a period of 5 minutes, but responded to intracardiac injection of Adrenalin, and artificial respiration with tracheal intubation and intermittent positive pressure oxygen.

sis which showed no response to intravenous injection of ⅙ M lactate solution or sodium bicarbonate solution.

Death occurred at the age of 38 hours.

Biochemical estimations on donor blood for the third exchange

Plasma potassium = >20 mEq./L. (Colorimeter standardized to 20 mEq./L.)

CO_2 combining power = 7.7 mEq./L.

pH = 6.1

Biochemical estimations on infant's blood

Before third exchange transfusion

Potassium = 4.3 mEq./L.

At time of cardiac arrest

Potassium = 12.0 mEq./L.

At time of cardiac arrest

Calcium = 3.5 mEq./L.

At time of cardiac arrest

CO_2 combining power = 12.2 mEq./L.

Fig. 5.—Case 2. Lead I. Time from start of exchange—27 min.; volume of blood injected—80 c.c.; normal nodal rhythm, rate—156 per minute.

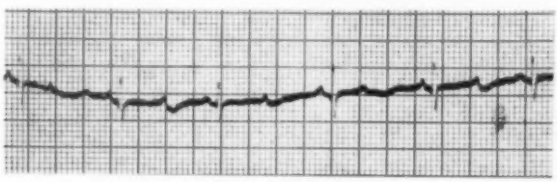

Fig. 6.—Case 2. Lead I. Time from start of exchange—27 min.; volume of blood injected—185 c.c.; slow nodal rhythm, rate—80 per minute.

For the remaining 14 hours of her life the infant remained in a precarious condition. She was nursed in a high concentration of oxygen, but her respiratory rate became irregular with intermittent periods of apnea and cyanosis. Her serum biochemistry showed evidence of a persistent acido-

Autopsy.—This was performed 12 hours after death. There was a slight icteric tinge to the skin as well as subconjunctival hemorrhages and petechiae over the trunk. Petechial hemorrhages were also seen subpleurally in the region of the trachea and lungs, in the heart, kidneys, and liver. The

lungs were hemorrhagic in appearance in the lower portion and fleshy in consistence. Microscopic examination revealed areas of extramedullary hematopoiesis, which were marked in the liver but also present in the kidney. Hemorrhages were present within the lung, kidney, thymus, and adrenal. The lungs showed moderate atelectasis. Sections of the heart showed no remarkable histopathological change.

The causes of death were finally designated, according to their presumed degree of importance, as follows: (1) post-transfusion electrolyte imbalance; (2) hemolytic disease of the newborn; (3) prematurity; (4) hypoxia; and (5) pulmonary atelectasis.

CASE 2.—*Cardiac Arrhythmia During Exchange Transfusion.*—

Experience with electrocardiography in 50 exchange transfusions performed on 36 infants has revealed one other example of gross cardiac arrhythmia. This infant weighed 2,160 Gm. and was of 35 weeks' gestation. The cord blood hemoglobin was 7.0 Gm. per cent and the bilirubin 6.82 mg. per cent. He received an exchange transfusion at the age of 1 hour, using 5-day-old partially packed blood. After injection of 185 c.c. of blood in 15 c.c. aliquots, the heart rate was suddenly slowed although the infant's general condition remained satisfactory. The ECG showed marked sinus bradycardia and occasional ectopic beats (Figs. 5 and 6). The arrhythmia was uninfluenced by injection of 1.5 c.c. calcium gluconate (10 per cent solution) and persisted until the end of a cautiously executed exchange of 450 c.c. of blood. The bradycardia alternated with periods of normal ECG configuration. ECG tracings taken on the first, second, third, and seventh days after the exchange transfusion were not remarkable and the infant's subsequent progress was uneventful.

Biochemical estimations on donor blood

Potassium = 9.7 mEq./L.
Calcium = 5.2 mEq./L.

Biochemical estimations on infant's blood

Before exchange transfusion
Potassium = 6.9 mEq./L.
Calcium = 5.0 mEq./L.
Mid-transfusion
Potassium = 5.1 mEq./L.
Calcium = 6.6 mEq./L.
Post-transfusion
Potassium = 7.6 mEq./L.
Calcium = 8.6 mEq./L.

The high figures for calcium in the mid- and post-transfusion samples could be due to contamination from immediately preceding injections of calcium gluconate solution.

DISCUSSION

Two examples of 2:1 auriculoventricular heart block detected by electrocardiographic examination during exchange transfusion have been reported by Joos, Yu, and Miller[3] (Table I). One infant, transfused with donor blood containing a plasma potassium of 8.0 mEq./L., developed parasystoles and 2:1 block intermittenly during the fourth and fifth 100 c.c. of the exchange. The arrhythmia was uninfluenced by calcium administration and the infant's serum potassium did not rise above 5.40 mEq./L. The second infant, a premature weighing 1,190 Gm., was transfused with donor blood containing a plasma potassium of 18.6 mEq./L. Arrhythmia consisting of 2:1 heart block developed during administration of the second 50 c.c. of exchange, persisted for 4 minutes, and then reverted to normal rhythm following the intravenous injection of 0.1 Gm. of calcium gluconate. The serum potassium just before the onset of the 2:1 block was 9.12 mEq./L. This baby died within 24 hours of the exchange transfusion. Autopsy revealed the findings of prematurity, severe hemolytic disease of

the newborn, and kernicterus. The heart was not abnormal.

Examples of cardiac arrest during exchange transfusion have been reported by Walker and Neligan (1 case).[4] Pew (1 case),[5] and Bolande, Traisman, and Philipsborn (4 cases).[6] These cases are summarized in Table I. Campbell[7] in a study of potassium levels in exchange transfusion has referred to 7 deaths in association with the transfusion. In 4 of these cases the infant's maximum potassium level ranged between 6.13 and 10.23 mEq./L. manifested itself with clinical signs of pulmonary or cardiac distress, which have included rapid respiratory rate, cyanosis, pulmonary crepitations, gagging, and production of frothy mucus. In contrast to this, the clinical state of the infants, referred to in Table I, was such that no anxiety was felt regarding their condition until the sudden onset of the cardiac manifestations. It is most likely that these infants suffered from a complication of exchange transfusion other than that of congestive heart failure.

TABLE I. A COMPARISON OF BIRTH WEIGHT, VOLUME OF BLOOD TRANSFUSED, AND BLOOD CHEMISTRY IN REPORTED CASES SHOWING CARDIAC ARRHYTHMIA OR ARREST DURING EXCHANGE TRANSFUSION

AUTHOR	WT. OF BABY (GM.)	VOL. OF BLOOD INJECTED BEFORE CARDIAC ARREST OR ONSET OF ARRHYTHMIA (C.C.)	DONOR BLOOD POTASSIUM (MEQ./L.)	INFANT BLOOD AT TIME OF CARDIAC ARREST OR END OF EXCHANGE		CALCIUM GIVEN DURING EXCHANGE
				POTASSIUM (MEQ./L.)	CALCIUM (MEQ./L.)	
With Electrocardiography						
Case 1	2,220	60	>20.0	12.0	3.5	Yes
Case 2	2,160	185	9.7	7.6	8.6	Yes
Joos, Yu, and Miller[3]	—	400	—	4.63	—	Yes
Joos, Yu, and Miller[3]	1,190	75	18.6	9.12	3.2	Yes
Without Electrocardiography						
Walker and Neligan[4]	2,400	230	16.52	14.58	—	No
Pew[5]	—	350	—	4.5	2.85	Yes
Bolande et al.[6]	—	—	9.55	5.16	—	Yes
Bolande[6]	—	—	22.70	5.30	—	Yes
Bolande[6]	—	—	21.10	6.55	—	Yes
Bolande[6]	—	—	20.50	7.75	—	Yes

Table I shows an analysis of 10 infants who shared in common the electrocardiographic features of sudden onset of arrhythmia, 2:1 heart block, or the clinical features of sudden cardiac arrest. In so far as it can be ascertained from reading the reports of these cases, it seemed unlikely that any of them suffered from the type of congestive heart failure described by Walker and Neligan,[4] and Allen and Diamond.[1] Congestive heart failure in hemolytic disease of the newborn can be an insidious process but has usually

There was no definite evidence other than the clinical features and the electrocardiographic findings that the mechanism of the cardiac arrhythmia was the same in all 10 cases. Case 1 which showed a sudden progression from a state of slow nodal rhythm, without associated clinical features, to complete cardiac arrest in a period of 4 minutes suggested that there was a possible interrelationship in this group of cases. It seemed likely that in this case there was some biochemical derangement or other factor which,

acting over a short period of time, severely embarrassed the heart action. Hyperpotassemia was not considered to be a likely cause. Serum potassium levels up to 7.8 mEq./L. have not been considered unusual (McCance and Young[8]) during the normal newborn period. Sudden cardiac arrest occurred with a potassium level as low as 4.5 mEq./L. in the infant reported by Pew.[5] In addition, Bolande[6] has reported 1 infant with a serum potassium of 17 mEq./L. who did not develop cardiac arrest during exchange and who survived the exchange transfusion for a period of 17 hours. A comparison of the potassium in the donor blood and the potassium in the infant's circulation in Table I suggested that most infants could handle comparatively large loads of infused potassium. This confirmed the observations of Campbell[7] and of Bolande.[6]

The possibility of cardiac arrest from hyperpotassemia also appeared unlikely from the experimental work of Baker and his co-workers.[9] They have reported the use of potassium citrate in the arrest of the perfused isolated hearts obtained from 4 stillborn fetuses of 16 to 20 weeks' gestation. A concentration of potassium citrate equivalent to 14.8 mEq./L. (calculated as tripotassium citrate) had to be directed as a continuous infusion into the coronary circulation to produce cardiac arrest. The volume of the potassium citrate solution required to produce this effect was not specified. Effler and his co-workers[10] have reported the use of potassium citrate solutions equivalent in strength to 230.0 mEq./L. (calculated as tripotassium citrate) and 6-20 c.c. volume to produce cardiac arrest in children undergoing cardiac surgery. In both reports the potassium solutions were directed into the coronary arteries and there was no opportunity for dilution to occur from mixture with venous blood. They have not, however, reported on the efficacy of weaker solutions of potassium. In exchange transfusion, the donor blood has ample opportunity to become diluted with the infant's venous blood before being directed to the coronary circulation.

Hypocalcemia was also considered as a cause of cardiac arrest. In 9 out of the 10 cases, calcium was given as a prophylactic measure during the exchange transfusion. In 2 cases of heart block and one of cardiac arrest, there was no response to immediate administration of calcium. It appeared unlikely, therefore, that calcium deficiency per se was the cause of the cardiac phenomena.

Pew[5] drew attention to the fact that his case of cardiac arrest followed shortly after the introduction of a bottle of cool blood into the exchange transfusion and that the heart felt cold when it was massaged. In Case 1 no attempt was made to warm the blood other than allowing it to stand at room temperature for about 10 to 15 minutes. Information with regard to warming of the blood is not available on the other cases. Hoff and Stansfield[11] and Deterling and his co-workers[12] have provided experimental evidence in the dog that ventricular fibrillation could develop when the body temperature was reduced below 73° F. or the local ventricular temperature below 50° F.

One factor which has not been given much consideration in previous reports is the effect that the acid-citrate dextrose anticoagulant mixture

has on reducing the pH and CO_2 combining power of donor blood. On samples of donor blood tested at this hospital, the average pH was 6.2 and this level varied little with the duration of storage. In Case 1, severe and irreversible acidosis was an outstanding feature following the third replacement transfusion. Deterling[12] demonstrated that the ventricular fibrillation induced in dogs by hypothermia did not develop when the blood was maintained in a state of alkalosis by hyperventilation.

At the present time it is not possible to state that any one specific factor or combinations of factors is responsible for the occurrence of cardiac arrest in infants undergoing exchange transfusion. According to circumstances several or all of the following factors may be present: hyperpotassemia, hypocalcemia, cooling of the heart, acidosis, prematurity, and the disease process of hemolytic disease. There may be other factors at present unsuspected. The combined use of electrocardiography and adequate biochemical study is one way of further elucidating the problems involved and, at the same time, ensuring maximum safety for the infant.

SUMMARY

Attention is drawn to the fact that sudden and unexpected death may occur during or shortly after exchange transfusion for hemolytic disease of the newborn.

One case is reported of bradycardia, ventricular fibrillation, and cardiac arrest after 70 c.c. of blood had been exchanged. A second case is reported of bradycardia and arrhythmia developing after an exchange of 185 c.c. of blood.

These cases are compared with 8 other case reports in which there is a similarity of clinical or electrocardiographic findings. It is not possible from the data available to determine a common etiological factor for the sudden alteration in cardiac function.

It is suggested that possible factors which might be operating singly, or in combination, are hyperpotassemia, hypocalcemia, hypothermia, acidosis, prematurity, and the disease processes of hemolytic disease.

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STUDIES ON FETAL LIVER FUNCTIONS IN HOMO- AND HETEROSPECIFIC PREGNANCIES WITH SPECIAL REFERENCE TO THE ICTERUS PRAECOX OF THE NEWBORN

I. Halbrecht, M.D., Petah Tiqua, Israel, M. Brzoza, M.Sc., and M. Lahav, M.Sc., Tel Aviv, Israel

CONTRARY to the great attention given during the last fifteen years to the pathogenetic role of the Rh factor in causing hemolytic disease of the newborn, relatively little attention has been paid to the A and B blood groups as a cause of this disease. This, despite the fact that not later than five years after the discovery of the ABO blood groups by Landsteiner, Dienst[1] first drew attention to the eventual damage that the ABO blood group incompatibility may cause to the mothers bearing children with blood groups incompatible with their own blood groups.

In 1923, Ottenberg[2] re-emphasized Dienst's conception, and two years later the definition of homo- and heterospecific pregnancies was coined by Hirszfeld and Zborovski, who again emphasized the damaging results of the antigen-antibody reaction in mothers and fetuses in heterospecific pregnancies.

The conception of these investigators has not been substantiated by subsequent investigations. It was not until 1945 that Polayes[3] first drew attention to the role of ABO blood group incompatibility in causing erythroblastosis fetalis in the newborn. Almost simultaneously we described (1944) the new clinical form of the hemolytic disease of the newborn, for which we proposed the name of "icterus praecox" and which has since been accepted by most authors.

In our previous communications,[4-6] we described in detail the clinical aspects of this mild variant of the hemolytic disease of the newborn which is mainly, but not exclusively, due to the ABO blood group incompatibility between mother and fetus.

During the past fifteen years we have been able to observe 190 cases of icterus praecox which appeared with a frequency of approximately 1 case in 120 to 130 deliveries.

Several conceptions have since been advanced by different authors to explain the striking difference in the gravity of the hemolytic disease of the newborn caused by the incompatibility of the Rh and ABO factors. These differences are the more surprising in that they are in contrast to expectations of what should really happen.

It is generally understood that the ABO and Rh systems are entirely independent of each other. It is furthermore evident that from the immunological point of view the former system is much more complete than the latter. Consequently we should expect to see more frequently severe reactions in

From the Department of Obstetrics and Gynecology, Hasharon Hospital, Petah Tiqua, Israel, and the Central Laboratories of the Kupat Holim, Tel Aviv, Israel.

ABO blood group incompatibilities than in cases of incompatibilities of the Rh factor. Not only has the ABO system naturally occurring antibodies which are lacking in the Rh system but, in addition, hemolysins and opsonins are always found in the blood of the mothers of newborn infants with hemolytic diseases caused by heterospecific pregnancies, whereas they are rarely, if at all, found in the maternal blood in Rh incompatibility.

The problem is further complicated by the presence of two variants of the A and B agglutinogens in the tissues and body fluids in secretors and of at least one, water-soluble variant in nonsecretors among the newborn infants, whereas the existence of a similar Rh substance in the tissues of the infants is denied by most investigators.[7-9]

In addition, changes in the osmotic fragility seem to be a characteristic feature of the fetal erythrocytes in heterospecific pregnancies, and microspherocytosis has been found exclusively in the syndrome of hemolytic diseases of the newborn caused by ABO blood group incompatibility.

In our first communication on icterus praecox we advanced the hypothesis explaining the mildness of the hemolytic disease of the newborn in heterospecific pregnancies by the presence of the A and B antigens in the tissues and body fluids of the newborn infant, especially in the secretor group, which neutralize the maternal alpha and beta immune antibodies circulating in the fetal blood. Plausible as this hypothesis seemed to us and to other authors, it has not been substantiated up to the present moment. Some investigators, on the other hand, have attributed damaging effects to the antigen-antibody reaction in the fetal tissues in cases of isoimmunization caused by heterospecific pregnancies.

The purpose of our present study was to investigate the liver functions of the newborns in homo- and heterospecific pregnancies with or without isoimmunization of the mothers by an ABO blood group incompatibility and to assess the degree of impairment of these functions resulting from an eventual antigen-antibody reaction in the fetal liver.

MATERIAL AND METHODS

Specimens of the cord blood of 120 newborn infants were examined and they were divided into the three following groups: *Group I*, 60 infants of homospecific pregnancies; *Group II*, 40 infants with blood groups incompatible with those of their mothers but without isoimmunization of the mothers against the ABO blood groups of the infants; *Group III*, 20 infants with icterus praecox due to the isoimmunization of the mothers against the ABO blood groups of their children.

A. *The total protein* concentration was determined in the serum of the cord blood by the biuretic method with the Kingsley modification for the separation of the albumin from the globulin, and an analysis of the different protein fractions was made by the paper electrophoretic method.

B. *The total bilirubin concentration* as well as the direct and indirect van den Bergh reaction was determined in the cord blood of all the newborn infants.

C and D. In addition, the *total cholesterol* and a battery of the following tests, generally considered as being related to the liver functions, have

been determined in the cord blood serum: (1) The *Weltman coagulation band;* (2) the *cephalin-cholesterol flocculation test;* (3) the *thymol turbidity* and *flocculation tests;* and (4) the *Lugol test.*

RESULTS

A. *Proteins.*—

1. *Total proteins*: As shown in Table I, the mean value of the total protein concentration was found to be significantly lower in the blood sera of the newborn infants in heterospecific than in homospecific pregnancies and much lower in the blood of newborn infants with icterus praecox. These mean values were 5.99, 5.80, and 5.66 Gm. per cent in the three groups, respectively.

Table I. Mean Values of Total Protein, Albumin, and Globulin Concentrations in the Cord Blood in Homo- and Heterospecific Pregnancies With and Without Isoimmunization of the Mother

Group	Total proteins (Gm. %)		Albumins (Gm. %)		Globulins (Gm. %)		Albumin/globulin ratio
	Average	Ranges	Average	Ranges	Average	Ranges	
I. Homospecific pregnancies	5.99	(5.10-6.80)	3.97	(3.0-4.50)	2.02	(1.7-2.50)	1.97
II. Heterospecific pregnancies without isoimmunization	5.80	(5.1-6.7)	3.82	(3.1-4.4)	1.98	(1.4-2.6)	1.92
III. Heterospecific pregnancies with isoimmunization; icterus praecox	5.56	(4.9-6.6)	3.62	(3.1-4.3)	1.94	(1.6-2.5)	1.86

2. *Electrophoretic pattern*: The electrophoretic pattern of the cord blood serum proteins, on the other hand, showed no significant differences in the distribution of the protein fractions in the three different groups of newborn infants. The mean values of the protein fractions in the cord blood sera, expressed in percentage, were: 62.8, 3.8, 7.4, 8.4, and 17.5 Gm. per cent for the albumin, alpha 1, alpha 2, beta, and gamma globulin fractions, respectively. This electrophoretic pattern of the cord blood serum proteins is very similar to the proteinogram of the normal adult but contrasts somewhat with the electrophoretic pattern of pregnant women at term. This pattern of the maternal blood serum proteins is characterized by a relatively high concentration of the alpha 2, beta, and gamma globulins and by a low concentration of the albumin fraction. (Table II.) The increased concentration of the alpha 2 and beta globulins may be explained by the increase of cholesterol and lipoproteins in the blood of pregnant women contrasting with the low concentration of cholesterol, lipids, and lipoproteins characteristic in the fetal blood.

B. *Cholesterol* (Table III).—The mean values of the cholesterol concentration in the cord blood were 82.5, 73.5, and 85.5 mg. per cent for the three groups of newborn infants, respectively. The lower mean value of the cholesterol concentration in the

TABLE II. ELECTROPHORETIC PATTERNS OF THE SERUM PROTEINS IN THE CORD BLOOD AND IN THE VENOUS BLOOD OF THE MOTHERS (IN PERCENTAGE)

		ALBUMINS	GLOBULINS			
			ALPHA	ALPHA 2	BETA	GAMMA
Newborn infants	Average	62.8	3.8	7.4	8.4	17.5
	Ranges	52-73	1-6	5-11	6-13	10-21.5
Mothers	Average	46.7	5.5	12.2	13.8	21.8
	Ranges	39-55	5-8	10-15	12-18	15-29

TABLE III. MEAN VALUES OF TOTAL CHOLESTEROL, TOTAL BILIRUBIN, AND DIRECT VAN DEN BERGH REACTION IN CORD BLOOD IN HOMO- AND HETEROSPECIFIC PREGNANCIES

GROUP	TOTAL CHOLESTEROL (MG. PER CENT)	TOTAL BILIRUBIN (MG. PER CENT)	DIRECT VAN DEN BERGH REACTION (PERCENTAGE)
I. Homospecific pregnancies			
Average	82.5	1.23	60
Ranges	65-128	0.3-3.8	
II. Heterospecific pregnancies			
Average	73.5	1.25	61
Ranges	60-105	0.3-2.1	
III. Icterus praecox			
Average	85.5	3.35	80
Ranges	55-113	0.9-7.5	

cord blood in heterospecific pregnancies (see Group II) does not seem to be significant enough and is, furthermore, in contrast with the mean value of the third group of newborn infants (heterospecific pregnancies with isoimmunization of the mothers) which was similar to the mean value of the first group, to permit us to draw any conclusion.

C. *Bilirubin.*—

1. *Total bilirubin*: The total bilirubin concentration was increased in the cord blood of almost all the newborn infants in comparison with normal values in healthy adults. The mean values of the bilirubin concentration were 1.23, 1.25, and 3.35 mg. per cent in the cord blood of the three groups of newborn infants, respectively. No difference in the bilirubin concentrations was therefore found between the homospecific and the heterospecific group without isoimmunization of the mother. The group of icterus praecox due to isoimmunization of the mother, on the other hand, was characterized by a very high bilirubin concentration in the cord blood. On the average, this concentration was almost three times as high as the mean value in the two other groups. The bilirubin concentration in the cord blood can therefore serve to predict, or at least to raise suspicion of, the appearance of icterus praecox in the newborn.

2. The *direct van den Bergh reaction*: This reaction was positive in 60, 61, and 80 per cent of the cord blood sera in the three groups, respectively, the mean values of the direct bilirubin concentration being 0.52, 0.46, and 0.92 mg. per cent for the three respective groups.

D. *Coagulation, Turbidity, and Flocculation Tests* (Table IV).—

1. The *Weltman coagulation* band showed a slight shift to the right in the blood of all the newborn infants, covering 7 to 8 tubes irrespective of

TABLE IV. COAGULATION FLOCCULATION AND TURBIDITY TESTS IN CORD BLOOD IN HOMO- AND HETEROSPECIFIC PREGNANCIES

GROUP	WELTMAN COAGULATION BAND (NUMBER OF TUBES)	CEPHALIN TEST POSITIVE REACTIONS (PER CENT)	THYMOL TURBIDITY (UNITS)	LUGOL TEST
I	7-8	50	0.73	Neg.
II	7-8	65	0.64	Neg.
III	7-8	76	1.50	Neg.

the group to which they belonged, with the exception of two cases of icterus praecox in which the coagulation band showed an extreme shift to the left covering no more than 1 to 2 tubes.

2. The *cephalin-cholesterol flocculation test* gave positive results in 50 per cent of the cord bloods of the homospecific group of pregnancies, in 65 per cent in the heterospecific group without isoimmunization of the mothers, and in 80 per cent of the group of newborn infants with icterus praecox.

3. The *thymol turbidity test* showed remarkably low values in the cord blood of all the newborn infants, but the mean value was definitely higher in the cord blood of those with icterus praecox. The mean values were 0.75, 0.65, and 1.50 units for the three groups, respectively.

The *thymol flocculation test* was negative in the cord blood of all the newborn infants.

4. The *Lugol test* was negative in the blood sera of all the newborn infants with very few exceptions, irrespective of the group to which they belonged.

DISCUSSION

None of the explanations so far given by different authors to elucidate the mildness of the hemolytic disease of the newborn caused by the ABO blood group incompatibility, contrasting with the severity of the same disease due to the Rh incompatibility, has proved to be satisfactory.

Neutralization of the maternal alpha and beta immune antibodies circulating in the fetal blood after having passed through the placental barrier, by the A and B antigens of the tissues and body fluids of the fetus, is still the most plausible conception hitherto brought forward.

Yannet and Lieberman[10] indeed found a significantly greater incidence of ABO blood group incompatibilities between children with mental deficiencies which could not be explained as postinfectious or posttraumatic, and their mothers, than between normal mothers and children. According to these authors, the mental deficiencies of these children may, partly at least, be explained by damage in the brain tissues caused by an antigen-antibody reaction.

Johnstone[11] found higher values of bilirubin concentration in the cord blood of heterospecific than in those of homospecific pregnancies. He too believes that an antigen-antibody reaction in the liver cells is the cause of the raised bilirubin concentration in the cord blood of heterospecific pregnancies.

The meaning of these observations seems to us to be that even the naturally occurring alpha and beta antibodies may have cytotoxic qualities, and it may be assumed that the immune antibodies of the ABO system possess these qualities to a much greater degree. Consequently, the

passage of these antibodies from the maternal to the fetal blood and their junction with the A and B antigens in the fetal tissues may have injurious effects on the respective organs.

Our findings corroborate to a certain degree the above-mentioned observations.

We did not find a more pronounced total bilirubin concentration in the cord blood in heterospecific pregnancies without isoimmunization of the mothers, than in the homospecific group. The percentage of the direct van den Bergh reaction was likewise identical in both groups of newborn infants. On the other hand, we found lower total protein concentrations and a higher percentage of positive cephalin reactions in the hetero- than in the homospecific group.

An eventual moderate degree of damage of the fetal liver tissues superimposed on the "physiological" immaturity of the fetal liver therefore cannot be excluded entirely in heterospecific pregnancies in general and in cases of isoimmunization of the mothers in particular.

The impairment of the fetal liver functions was especially evident in the newborn infants with icterus praecox. In the cord blood of these infants we found particularly low total protein concentrations, high bilirubin values, a very high percentage of positive van den Bergh reactions, and a much higher percentage of positive cephalin flocculation tests than in the cord blood of the other groups of newborn infants. In addition, we found, in two cases of icterus praecox, a shift to the extreme left of the Weltman coagluation band which is certainly not without significance.

At the present stage of our investigations no more can be said than that the impaired liver functions of the newborn infant probably play a much greater role in the pathogenesis of the hemolytic disease of the newborn than hitherto admitted. Whether the conspicuous impairment of the fetal liver functions in heterospecific pregnancies is the direct result of an antigen-antibody reaction in the fetal liver remains to be elucidated by further investigations.

SUMMARY

The liver functions of 120 newborn infants were determined by examination of the blood chemistry of their cord blood.

The influence of the heterospecific pregnancies on the liver functions of the infants was examined by comparing the blood chemistry of the cord blood in homo- and heterospecific pregnancies.

The mean values of the total protein concentrations were found to be lower in the cord bloods of the hetero- than in those of the homospecific group. It was especially low in cases of icterus praecox due to isoimmunization of the mother.

A high total bilirubin concentration and a high percentage of direct bilirubin reactions (80 per cent) were found in the cord blood of newborn infants with icterus praecox, but no difference between the degree of the "physiological" hyperbilirubinemia of the cord blood of homo- and heterospecific pregnancies could be found.

The cephalin flocculation test gave more frequently positive results in hetero- than in homospecific pregnancies.

The thymol turbidity test showed higher values in the blood of newborn infants with icterus praecox.

It is suggested that the ABO blood group incompatibility between mothers and children may be considered as being responsible for the impairment of the liver functions of the newborn in heterospecific pregnancies and especially in cases of isoimmunization of the mother.

Editorial Note: Recent evidence has demonstrated that the excretion of water-insoluble indirect bilirubin involves its conversion to a direct-reacting water-soluble pigment by conjugation with glucuronic acid. The formation of bilirubin glucuronide in the liver depends upon the transfer by an enzyme glucuronyl transferase. According to this concept, the newborn with physiologic jaundice is handicapped by a delay in the formation of bilirubin glucuronyl transferase at birth. The effect of this delay is most pronounced in erythroblastosis where red-cell breakdown is excessive, as a result of which the newborn infant is exposed to high plasma concentrations of indirect bilirubin.*

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PSEUDOMONAS AERUGINOSA INFECTIONS: REPORT OF TWO PATIENTS WITH MENINGITIS

ARCHIBALD L. HOYNE, M.D., SEYMOUR METRICK, M.D., AND TORU SAKUMA, M.D.
CHICAGO, ILL.

IT IS quite generally believed that pseudomonas infections (*Bacillus pyocaneus*) are more frequent and of greater severity now than some years ago. The change that has taken place is attributed to a modification of the bacterial flora in the body brought about by the extensive use of the antibiotics.[1, 2]

Pseudomonas aeruginosa infections have been assigned to various sources which include head injuries, extension from focus in ear or sinus, genitourinary conditions, operations for spinal cord tumor or laminectomy; also spinal anesthesia and intrathecal therapy. In 1947, Stanley[3] reported that, up to that time, 41 cases of primary *B. pyocyaneus* meningitis had been published; of that number, 32 (78 per cent) were the direct result of lumbar puncture. Infections of the umbilicus in the newborn have been recorded, possibly due to the organism being air-borne in the ward. A contaminated milk[4] supply has been incriminated also as being responsible for an epidemic in a newborn nursery where in 24 infants there were 9 deaths.

Skin lesions are common but none may occur. There may be only diarrhea,[4] which is bloody, and dehydration. But cutaneous lesions and hemorrhagic conditions are usually described in the severe cases[1, 2] and, in these, septicemia with positive blood cultures may be expected.

Because the vascular[5] system is likely to be attacked, numerous and often fatal complications follow. Necrosis may occur in any location of the entire gastrointestinal tract. Ecthyma gangraenosum may be a terminal complication.

Clement and Millard[1] state that meningitis is the commonest internal complication, the focus being otitis media, mastoiditis, or sinus infections. However, meningitis as a complication of *Ps. aeruginosa* infection is rarely reported in infants and it is extremely infrequent in adults. It is because of the latter situations that we believe our 2 patients are of unusual interest.

Abdominal distention[5] has been regarded as a characteristic finding in *Ps. aeruginosa* septicemia. Nevertheless, it was not evident in Case I. In the other instance (Case II), the patient's abdomen was tense but actual distention was not notable.

In both of our patients, petechiae were present in the skin. The child had more on the feet and ankles than in any other locality, but the man had petechiae more widely and evenly distributed over the entire surface of the body.

From Cook County Contagious Disease Hospital and Chicago Medical School.

Cutler and Cutler[6] have directed attention to a simple means of establishing a bacteriologic diagnosis in cases of Pseudomonas meningitis without awaiting a culture report. The procedure consists of exposing the spinal fluid to ultraviolet light. By doing so, "the spinal fluid even though colorless will show a greenish fluorescence." By resorting to this prompt method for identifying the organism, appropriate therapy can be instituted immediately.

It may be noted in the case histories that the child (Case I) was treated throughout with oxytetracycline although found to be more sensitive to streptomycin. The man (Case II) did not respond well to oxytetracycline; nor was polymyxin B effective. It was then disclosed by the laboratory that the infecting organism was more sensitive to Chloromycetin than to polymyxin B,[7] although the latter is often regarded as the drug of choice for combating *B. pyocyaneus* infections. But some investigators[1, 4] have found that almost immediate improvement may be gained by injections of 1.0 per cent methylene blue.

CASE REPORTS

CASE I.—On July 31, 1957, a 15-month-old Negro boy was hospitalized at Cook County Contagious Disease Hospital. He was said to be in good health until he developed fever one day prior to admission. A local physician saw him and prescribed pink tablets (sulfathiazole?). The mother stated she was directed to administer one tablet every 4 hours and did so on 3 occasions. Despite the medication, temperature elevation persisted and slight swelling of the face appeared. The following morning, the patient had two soft stools and one episode of emesis. The child was brought to the hospital in the early afternoon.

On admission, the temperature was 101° F., pulse was 120, respirations were 30, and blood pressure was 96/50 mm. Hg. The patient was a well-developed, well-nourished, male infant appearing acutely ill and slightly listless. The head was normal. There was slight puffiness about both eyes. Conjunctivae showed a few areas of punctate hemorrhage. Pupils and fundi were negative, bilaterally. Eardrums were seen with minimal injection but without drainage. A questionable nuchal stiffness was present. The heart and lungs were negative. Abdominal examination was unrevealing. There were scattered petechiae over the extremities, particularly prominent on both feet which were slightly edematous; there was, also, pretibial edema. Reflexes were normal. No Kernig or Brudzinski sign was detected.

Lumbar puncture was performed in view of possible meningococcemia with meningitis. Slightly turbid fluid was obtained. The cell count was 1,334 per millimeter, lymphocytes 1,243, polymorphonuclears 91. No organisms were seen on gram-stained smear. Additional laboratory data included hemoglobulin, 47 per cent; red blood count, 3,400,400; white blood count, 15,200 with differential neutrophils 64 per cent, band 15 per cent, lymphocytes 15 per cent, and monocytes 5 per cent. Cerebrospinal fluid showed glucose 57, protein 22, and chloride 107 milligram per cent. The Pandy reaction was positive. Later culture of spinal fluid specimen grew out *Pseudomonas aeruginosa* in two tubes, in one of which there was also *Escherichia coli*. Blood culture revealed enterococci. Urinalysis done repeatedly was negative for albumin, sugar, acetone and was negative, also, on microscopic examination. Blood serology for syphilis was negative. Bacterial sensitivity studies of antibiotics showed Pseudomonas and Escherichia to be sensitive to streptomycin, less so to tetracycline (10 to 50 meg.) and resistant to chloramphenicol (more than 50 meg.). Enterococci had susceptibility to erythromycin, tetracycline, chloramphenicol, and slight sensitivity to penicillin.

For approximately the first forty-eight hours, tetracycline, 75 mg. per kilogram of body weight, four times daily, was administered intravenously. This was followed by oral medication of similar dosage (125 mg.) every four hours. The clinical response to the regime was remarkable. The patient became completely afebrile on the fourth hospital day and remained essentially so thereafter. Slight puffiness on the face was observed as late as the sixth hospital day but subsided completely soon afterward. Otherwise, the patient was perfectly asymptomatic except for the existence of healing petechiae and few confluent necrotic lesions which were still evident over the extremities and hips during the last week of his hospital stay. The parents took the patient out of hospital against medical advice on Aug. 12, 1957, which was the fourteenth day after the onset of his illness. The child was symptom free at that time, after 12 days' treatment. In accord with a long-established custom in this hospital, there was no intrathecal therapy nor were lumbar punctures made for drainage.

CASE II.—*History.*—A 29-year-old white man was admitted to a medical ward of Cook County Hospital on Oct. 14, 1953. He was disoriented so that a completely coherent statement was not obtainable. However, the patient was able to relate that he had a sore throat, had been coughing for a week, and that during the past two days had experienced severe headaches and repeated attacks of vomiting. It was also ascertained that he had been drinking to excess during the past eleven years and he claimed to have had a similar illness in 1943 after drinking "White Lightning."

Physical examination revealed a well-developed white man of fair nourishment who was confused and somnolent. There was a diffuse macular rash, pink in color, which involved the surfaces of the entire trunk and extremities. The pulse was 94, temperature was 101° F., rectally, and blood pressure was 110/84 mm. Hg. The pupils were equal and reacted to light and accommodation. The conjunctivae were moderately injected. The fundi could not be visualized adequately. Nucal rigidity was marked. The heart and lungs presented no unusual findings. Abdominal examination was negative except for slight tenseness and hyperactive bowel sounds. Genitalia and rectal examinations disclosed no abnormalities. Brudzinski, Gordon, and Oppenheimer signs were positive on the left. On the same side, the patellar reflex was increased and ankle clonus elicited. There was weakness and carpopedal spasm of the left hand.

A lumbar puncture was performed and recorded an opening pressure of 300 ml. of water. Approximately 12 c.c. of purulent fluid was released. The closing pressure was 120 ml. of water. The cell count was 8,000 polymorphonuclears but a gram stain disclosed no organisms. The Pandy reaction was positive. The patient was then transferred to the Contagious Disease Department (Cook County Contagious Disease Hospital) where he was given tetracyline (Terramycin) immediately, 250 mg. intravenously, and supportive treatment. The same dosage and route for Terramycin therapy was continued every four hours for eight days.

Hospital Course.—On the second hospital day, the rash had entirely disappeared and the patient was much more rational. The laboratory report of chemistry for spinal fluid stated glucose was 75 mg. per cent and protein was 550 mg. per cent. Blood chemistry for chlorides sodium, total protein, and NPN were within normal limits. Serum K was 7.1. Blood serology and agglutination tests for typhoid, Brucella, and Salmonella were all negative. Due to an unforseen delay, the result of culture of the spinal fluid was not received until the eighth hospital day. Both *Pseudomonas aeruginosa* and *Aerobacter aerogenes* were reported. The blood culture was positive for nonhemolytic streptococci. Although the patient

had shown marked improvement clinically during eight days of Terramycin therapy, he continued to have a septic temperature. Treatment was then changed to streptomycin for two days without alteration of the fever pattern which ranged from normal to 103.8° F. orally. At this time a complete blood count was made; hemoglobin 95 per cent, leukocytes 14,500, with a shift to the left. Red blood count was 4,200,000.

An eye consultation did not reveal any signs of increased intracranial pressure. A spinal tap was made and 1,600 polymorphonuclear cells reported in the spinal fluid with glucose 35 mg. per cent and protein 130 mg. per cent. No organisms were seen on smear and culture was negative.

On the tenth hospital day, polymyxin B, 150 mg., daily in three divided doses intramuscularly, was substituted for streptomycin but septic temperature persisted. Urinalysis was performed daily including culture and blood NPN every other day. In the meantime, sensitivity tests had shown that *Pseudomonas aeruginosa* and *Aerobacter aerogenes* were more sensitive to chloromycetin than to Terramycin or to Aureomycin. After five days of polymyxin B therapy without change in the fever curve, Chloromycetin was substituted as a remedy and administered orally, 250 mg. every six hours. Within twenty-four hours following the institution of this therapy the temperature receded to normal and remained so. Four days later (the nineteenth hospital day) all medication was discontinued. A final lumbar puncture was performed on the twenty-first hospital day and the spinal fluid was found to be normal in all respects except for a slight elevation of protein. The patient was discharged completely asymptomatic on the twenty-third hospital day.

COMMENT

We wish to emphasize that neither of the 2 patients received any intrathecal therapy; nor were spinal taps performed for drainage[8] to "relieve intracranial pressure." However, for any form of meningitis, sensitivity tests should be made for several of the remedial agents in order to determine whether the drug being employed is the most effective. Both patients recovered without complications and their treatment was not beset with unnecessary procedures which sometimes prove to be harmful.[9] Fatality rates for groups of patients with *Ps. aeruginosa* meningitis have ranged from 55 per cent to approximately 90 per cent.

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MENTAL DEFICIENCY, SPASTICITY, AND CONGENITAL ICHTHYOSIS

Report of a Case

Joseph K. Link, M.D., and Erlinda C. Roldan,* M.D.
Buffalo, N. Y.

A SYNDROME consisting of a triad of mental deficiency, quadriplegia, and ichthyosis was first reported by Sjogren and Larsson in Sweden in 1955. Prior to this, however, Laubenthal, in 1938, described a monozygotic pair of female twins with idiocy, congenital ichthyosis, and a positive Babinski sign. To the best knowledge of the authors this condition has never been reported in the American literature nor in individuals other than those of Swedish origin.

The object of this paper is to report a case of a 7-year-old white boy with manifestations of this syndrome and to review the reports of the two mentioned Swedish authors.

CASE REPORT

L. M. W., white male, born June 21, 1950, was the first-born child of German and Italian parents. Except for the presence of diabetes in the maternal grandfather, the family history is negative. There is no history of cerebral palsy, familial skin condition, or mental retardation in either immediate or distant relatives. The mother has had no stillbirths or miscarriages. There is one normal sibling.

The mother's pregnancy was uneventful. The delivery, one month prematurely, was rapid and spontaneous. The anesthesia was a general ether anesthesia and she was given one injection of an unknown medication. The birth weight was 5 pounds 7 ounces. The baby was apparently normal at birth except for generalized ichthyosis. At the age of 2 days, he was placed in an incubator. He was bottle fed and given vitamins. He nursed well and occasionally regurgitated part of his feedings. Solid foods were started at the age of 3 months and he was weaned from the bottle at 14 months of age.

Because of the congenital ichthyosis, the child was followed closely by the family doctor. At the age of 4 months, the mother noticed it was hard for her to spread the baby's legs apart while changing the diapers. She also observed that he was not progressing normally and had a poor sense of balance. He sat alone at 2 years but has never stood or walked alone. At the age of 18 months, another doctor was consulted who recommended an x-ray study of the legs; this was reported to be negative. A diagnosis of cerebral palsy was made after 12 days' hospitalization at about 20 months of age. Braces were advised and at the age of 2 years he was given physiotherapy which was continued until the summer of 1957 at which time he had surgical adductor release of both legs. He gradually improved through the years until he could take a few steps with crutches. However, he still preferred a wheel chair.

He first used sentences at the age of 6 years. He had some speech impediment but no speech therapy was

From the Department of Pediatrics, Edward J. Meyer Memorial Hospital, and School 84 for Crippled Children, Buffalo, N. Y.
*Fellow, Sister Elizabeth Kenny Foundation.

advised. The rest of his past history included measles, tonsillectomy, and adenoidectomy at 5 years of age and a laceration of the neck which was sustained after a fall at the age of 6½ years. There was no history of convulsive seizures. The skeletal growth has been within normal range.

When first seen at Public School No. 84 (the school for the handicapped children at the Edward J. Meyer Memorial Hospital) in September, 1957, the physical examination revealed an uncooperative 7-year-old white boy in a wheel chair whose attention span was short and who cried throughout the examination. The head circumference was 20 inches and the frontal bones were prominent. His eyes were rather wide apart, the palpebral fissures small, and he had a right exotropia. The fundi were normal. The ears were negative and he had enlarged inferior turbinates. The teeth were irregular in shape and the occlusal surfaces were serrated. His palate was rather highly arched, his neck supple. The chest circumference was 24½ inches. There were no spine deformities and his heart, lungs, abdomen, and genitals were normal for his age. The skin of the face was flushed, especially about the cheeks, and a generalized ichthyosis was present with minimal scaling. The skin of the extremities showed a greater degree of desquamation.

Spasticity which was evident in all extremities was slightly more marked in the legs. The deep tendon reflexes in the upper limbs were physiological. Both hands were broad and the fingers were chubby. The lower extremities showed hyperactive deep tendon reflexes and marked ankle clonus. Bilateral Babinski signs were elicited. The right lower limb was 23½ inches in length and the left was 24 inches. A slight bowing of the legs was noted.

A Binet L test done in September, 1957, revealed an intelligence quotient of 54.

DISCUSSION

Twenty-eight cases of this syndrome have been reported in Sweden by Sjogren and Larsson. This syndrome consists of the following triad of physical abnormalities: (1) congenital, low-grade oligophrenia; (2) congenital pronounced ichthyosis; and (3) congenital, symmetrical, spastic pyramidal symptoms in the extremities, especially the legs. Four of these patients died before the age of 3 years and 10 died at older ages. Of the 24 patients, 22 were from the county of Vasterbotten, the second most northerly county of Sweden and the other 2 were from Engeniabement in Stockholm. The latter 2, however, had ancestral lines to Vasterbotten. The spastic disorders are those found in typical cases of Little's disease with one exception. In the majority of cases the mental deficiency was on the idiocy level (IQ up to 30) and the rest were imbeciles (IQ up to 50). Various grades of paralysis from minimal to marked was generally present, always associated with hypertonus of the limb musculature. Most patients had increased deep tendon reflexes and a positive Babinski sign. The ichthyosis was congenital in all and was clinically and histologically similar to congenital ichthyosiform erythroderma. Other manifestations which have been described by Sjogren and Larsson in their cases were the following: degeneration of the epithelium of the macula and its surroundings (in 3 cases); atrophy of leg muscles (9 cases); slow tremors in the hands (in 3 cases); gradually deteriorating gait (in 4 cases); and 1 case with convulsions. Because of the degree of mental retardation, vision could not be properly evaluated. Sexual development was reported to be normal.

There are no significant laboratory abnormalities in this syndrome. The

diagnosis can be made solely on clinical grounds because the picture is quite distinctive, although the manifestations show variation in all three main symptoms.

It is assumed that a single recessive gene mutation is responsible for this syndrome. Exogenous factors like premature birth, difficult delivery, and infections in infancy apparently have no significance in the causation of this syndrome.

There is no recognized treatment for this condition. As far as the prognosis is concerned, Sjogren and Larsson reported that all their patients were totally incapacitated and none of them married and none had children. The mean expectation of life for those affected did not exceed half that of the general population.

SUMMARY AND CONCLUSIONS

A case of mental deficiency, spasticity, and congenital ichthyosis in a 7-year-old white male of German and Italian extraction is reported and a review of the available Scandinavian literature is presented.

REFERENCES

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2. Mental Defect, Tetraplegia and Ichthyosis, Lancet 2: 337, 1957.

I have just seen the operation of transfusion, in a case of malignant cholera, performed by Dr. F. T. Ferris. The subject was Mrs. Rice, No. 105 Broome street, about 50 years of age.

Before the operation was performed, this female appeared to be in the last stage of disease; she had lost the power of speech; she had no pulse; her extremities and tongue were cold; her hands and feet blue, and her whole appearance indicated immediate dissolution.—Dr. Ferris was in attendance, and as the last resort performed the operation of transfusing into the veins a quantity of warm water, impregnated with muriate and sub carbonate of soda. The breathing became natural, the pulse gradually appeared at the wrist, the heat of the surface was restored, the natural color of the skin re-appeared, her voice became natural, and in fact she was *literally restored from death to life.* Her eyes, from being glassy and death-like, became natural and sprightly; her voice was strong, and she actually began to direct some of the domestic concerns of her family. I left her about two hours after the operation had been commenced, expressing her gratitude to the doctor, for his exertions, and thanking her God for her comparative restoration.

I send you this hasty account of the operation for publication, hoping the doctor himself will soon give a more minute detail of the case.

H. M. D.

FROM THE AMERICAN MERCURY (Hartford, Connecticut) July 30, 1832. (Apparently copied from some New York newspaper.)

A RELIABLE PAPER-STRIP METHOD FOR THE DETECTION OF PHENYLKETONURIA

HENRY W. BAIRD III, M.D.
PHILADELPHIA, PA.

UNTIL 3 years ago, prompt recognition of phenylketonuria was relatively unimportant. However, recent reports indicate that effective dietary management, started early in life, can prevent the severe mental retardation usually associated with this condition.[1, 2, 3] The incidence of phenylketonuria is so low (1 in 20,000 live births) that a quick but reliable screening test is essential if the diagnosis is to be made frequently before evidence of retardation develops.

A screening test for the detection of phenylketonuria should require a small amount of urine, be relatively independent of cumbersome collection, and have a readily apparent color change when 30 mg. per cent or more of phenylpyruvic acid is present in the urine. A reliable paper-strip method would have the additional advantages of speed and convenience. In our hands, a technique which utilizes a chemically treated paper stick fulfills these criteria satisfactorily.

METHOD

Suitable test material was prepared by impregnating a portion of a paper stick (¼ by 2 in.) with ferric chloride and glacial acetic acid and allowing it to dry.* A positive reaction was said to have occurred if the chemically treated portion of the paper turned green, gray, or dark blue within 60 seconds of its immersion in the solution submitted for examination. In serial dilution tests, four or more observers interpreted the reactions independently. Two individuals had had no previous experience with either the paper or the tube method. The latter test is performed by observing the color formed following the addition of 5 per cent ferric chloride to a solution acidified by glacial acetic acid. A blue-green or black color indicates the presence of phenylpyruvic acid; a brown or white color bears no relationship to its presence.

The paper strips were tested in four ways.

A. Solutions containing known but varying amounts of phenylpyruvic acid in distilled water were tested separately by the paper and the tube methods.

B. A stock solution of 100 mg. per cent of phenylpyruvic acid in distilled water was diluted with urine of non-phenylketonurie children. Solutions containing known but varying amounts of phenylpyruvic acid in urine from

From the Department of Pediatrics, Temple University School of Medicine and St. Christopher's Hospital for Children.

*After initial tests had indicated their practicability, these sticks were supplied in an improved form by Ames Laboratories, Elkhart, Ind.

6 nonphenylketonuric children were tested by each method.

C. Specimens of urine from patients known to have phenylketonuria were tested by each method. Some of these specimens had been voided 5 to 10 minutes previously; others had been frozen and stored for periods up to 16 months. All specimens were allowed to stand at room temperature and were tested periodically until both the paper and the tube tests became negative.

D. The results of periodic tests with the paper strips were recorded on one phenylketonuric child after her usual diet had been replaced by one containing not more than 15 mg. per kilogram of body weight of phenylalanine per day. Determinations of the phenylalanine levels in the serum and in the 24-hour urine specimens were made periodically until the paper and tube tests for phenylpyruvic acid became negative.

RESULTS

A. A light green color appeared on the test strip after it had been dipped in solutions containing 5 to 10 mg. per cent of phenylpyruvic acid in distilled water. This color change was readily apparent to inexperienced observers in solutions containing 10 mg. per cent. By the test tube method, inexperienced observers recorded positive readings in solutions containing up to 20 mg. per cent. With practice, a color change could usually be detected by the tube method in solutions containing 10 to 15 mg. per cent.

B. Definite color changes were apparent by the paper method in solutions containing urine with known amounts of 30 mg. per cent or more of phenylpyruvic acid. In some instances, 20 mg. per cent could be easily detected by inexperienced observers. Clearly definite color changes were apparent by the tube method in solutions containing from 20 mg. per cent to 40 mg. per cent, depending upon the experience and skill of the investigator. In solutions with concentrates of phenylpyruvic acid of 15 to 30 mg. per cent, the color changes on the paper strip were easier to interpret in each instance than were those in the test tube.

C. Twenty-five specimens of urine from phenylketonuric patients were positive initially by both methods. These specimens were tested repeatedly for 6 to 72 hours until the paper test was only faintly positive. At this time, the tube method was frequently indeterminate. In every instance, the color change was apparent for a longer time on the paper than in the tube.

D. *Low Phenylalanine Diet.*—During an observation period of one week prior to the institution of a low phenylalanine diet for an affected child, determination of the phenylalanine level in four 24-hour urine specimens varied from 30 to 40 mg. per cent. Four determinations of the concentration of phenylalanine in the serum varied from 40 to 50 mg. per cent. Two days after the diet had been instituted, the level of phenylalanine in the serum was 35 mg. per cent, and in the 24-hour urine, 40 mg. per cent. The test strips were positive until the sixth day. The concentration of phenylalanine in the serum was 15 mg. per cent both before and after the collection of a 24-hour urine on the sixth day. This specimen of urine contained less than 5 mg. per cent of phenylalanine.

False positives, which can be expected if excessive amounts of bilirubin are excreted in the urine, were not encountered.

DISCUSSION

The chemical defect of an affected person is reflected in his inability to oxidize adequate amounts of phenylalanine into tyrosine and therefore in the production of increased amounts of other metabolic end products. One of these is phenylpyruvic acid which usually appears in the urine if the level of phenylalanine in the serum exceeds 20 mg. per cent. Because all known phenylketonuric children over 34 days of age excrete more than 30 mg. per cent of phenylpyruvic acid in random specimens, a method which shows this amount consistently appears to be satisfactory for screening purposes. Our experience with the paper-strip method indicates that it is superior to the test tube method and is more easily performed. The addition of ferric chloride and acetic acid in the tube method tends to dilute the solution further and may account for the consistent finding that paper strips are more likely to be positive in solutions containing small amounts of phenylpyruvic acid. In addition, the slight color changes remain on the paper until it dries thoroughly, but with the tube method a faintly positive color change quickly fades.

The detection of an affected infant early in life and the maintenance of his serum phenylalanine level at less than 5 mg. per cent probably prevents significant motor or mental retardation. At present, the only reliable method of regulating the amount of phenylalanine in the diet of an affected patient is the period examination of the serum for phenylalanine.

If the presence of phenylketonuria is suspected because a previous sibling is affected, determinations of the amounts of phenylalanine present in the serum during the first month of life are desirable. In other infants, the urine should be tested between 6 weeks and 4 months of age. Enough urine to saturate the paper strip is easily obtained either from a wet diaper or, preferably, from a freshly voided specimen. A positive result is so easily recognized that a test strip can be given to most mothers if necessary. It is obvious that the test should be repeated in any infant whose mental development is slow.

SUMMARY

A paper-strip method for detection of phenylketonuria has been found reliable and practical. Its routine use at the time of the first and second well baby visit is suggested.

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THE MECHANICS OF ESTABLISHING A POISON CONTROL CENTER IN A COMMUNITY HOSPITAL

SAMUEL C. SOUTHARD, M.D.,* WALTER B. STEWART, M.D., AND
WILLIAM F. MATTHEWS, M.D.
ATLANTIC CITY AND MONTCLAIR, N. J.

RECENT advances in pediatric therapy have improved mortality and morbidity statistics to the point that accidents have become the leading cause of death and injury in childhood. The five most common fatal accidents are falls, burns, poisoning, firearm accidents, and drowning. Among these, poisoning lends itself best to an organized approach. This has led to the unique development of poison control centers, in which Dr. Edward Press has been a pioneer.

The purpose of this paper is to present the necessary steps in organizing a poison control center in a community hospital. This type of center must be distinguished from the large programs operated by municipal or state governments. The average community hospital does not have sufficient funds for the maintenance of full-time salaried directors, assistants, toxicologists, and clerks. In our experience, a center can be operated efficiently, yet inexpensively, within the existing framework of the average community hospital, with an initial outlay of less than three hundred ($300.00) dollars. Our aim is to encourage and assist other hospitals in the establishment of poison control centers.

STEP I.—The first step is the appointment of a director and an assistant director who are members of the medical staff. Since the majority of accidental poisonings occur in children, the director should be a physician who devotes a large part of his time to pediatrics.

STEP II.—The second step is to determine the location of the center. The accident or emergency dispensary, which is already staffed and organized to handle urgent cases, affords the best spot in the average community hospital.

STEP III.—The third step is to determine the functions of the center and the best methods of implementing them.

The first function is the treatment and care of the poisoned patient. This requires the center to be prepared for even the most unusual type of poisoning. Necessary equipment, supportive drugs, and a large number of antidotes must be kept in one place, so that nurses will not have to scurry about the hospital from drug room to tray room and lose vital time in starting

From the Pediatric Services of Atlantic City Hospital, Atlantic City, N. J., and the Mountainside Hospital, Montclair, N. J.

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*Address: 7217 Atlantic Avenue, Atlantic City, N. J.

treatment. The personnel of the dispensary must be instructed and supervised frequently by the director.

The second function is to prevent future poisonings and to educate the community in accident prevention. The mere existence of the poison control center stimulates interest and brings the problem into focus. In Atlantic City, the newspapers have assisted materially by running pictorial feature stories of the activities of the Center, each story carrying a message to the general public. The bulletin of the County Medical Society has carried informative articles about the Center to the rural physicians, among whom it has created considerable interest. Talks on the radio and to P. T. A. groups and to service clubs are a part of the program. Follow-up visits by a nurse to the home of each poisoned patient are of great educational value in the prevention of future trouble.

CHART I. EQUIPMENT FOR POISON CONTROL CENTER

1. One cabinet, five feet high, with glass-paneled door
2. One file cabinet
3. Seven Levin tubes, various sizes
4. One atomizer
5. Four 50 c.c. syringes
6. Four adapters—to connect Levin tubes to syringes
7. One stomach pump, with bulb
8. One stomach pump, plain
9. Two liter pitchers
10. Two kidney basins
11. Needles and syringes for parenteral injections
12. Administration sets for intravenous fluids, plasma, and blood

The third function is the maintenance of records and assistance in the compilation of statistics. It is only through these figures that the State Department of Health, the Public Health Service, the National Clearinghouse, and the Federal Food and Drug Administration will be able to influence legislation, manufacturing, and merchandising toward the reduction of the poisoning hazard. The New Jersey State Department of Health compiles poisoning statistics based on reports from the various centers.

CHART II. POISON CONTROL ANTIDOTE AND DRUG LIST

- Acetic acid
- Aminophylline
- Amphetamine sulfate
- Amyl nitrite perls
- Apomorphine (hypo tablets)
- Atropine sulfate (hypo tablets)
- British anti-lewisite
- Brewer's yeast
- Bromobenzine
- Caffeine sodium benzoate
- Calcium EDTA
- Calcium gluconate, 10% for I.V. administration
- Calcium lactate solution for lavage, and oral administration
- Camphor in oil
- Codeine phosphate (hypo tablets)
- Coramine
- Cystine
- Digitalis
- Ephedrine sulfate
- Epinephrine HCl, 1-1000 solution
- 5% glucose in saline
- Glucose 50 c.c. of 50% solution in amps.
- Lime water
- Magnesium oxide
- Magnesium sulfate
- Metrazol for injection
- Milk, evaporated
- Morphine sulfate solution
- Neostigmine methyl salicylate
- Phenobarbital tablets
- Picrotoxin
- Pilocarpine HCl (hypo tablets)
- Potassium permanganate solution
- Procaine penicillin
- Procaine, plain
- Procaine amide
- Saline, normal solution
- Sodium Amytal
- Sod. bicarbonate powder
- Sod. formaldehyde sufoxalate
- Sod. nitrite solution, amp. 0.3 Gm. in 10 c.c.
- Sod. pentonucleotide
- Sod. thiosulfate solution, amp. 12.5 Gm. in 50 c.c. water
- Sod. thiosulfate
- Tannic acid
- Theophylline tablets
- Tr. opium
- Universal antidote
- Vitamins B, C, K

The fourth function is research. By study and analysis of the cases treated over a period of years, it is hoped that we may improve our techniques and save more lives.

STEP IV.—The fourth step is the securing of the necessary equipment, drugs, and antidotes.

The equipment used in our Center is listed in Chart I.

The drugs and antidotes are listed in Chart II.

STEP V.—The fifth step is obtaining a reference library. At the present time we use the following sources:

1. *Handbook of Pediatric Medical Emergencies,* second edition, by Adolph G. DeSanctis, M.D., and Charles Varga, M.D., published by The C. V. Mosby Company, St. Louis, Mo., in 1956.

2. *Clinical Toxicology of Commercial Products,* by Marion N. Gleason, Robert E. Gosselin, M.D., and Harold C. Hodge, Ph.D., D.Sc., published by the Williams and Wilkins Company, Baltimore, Md., in 1957.

3. *Handbook of Poisons* by Robert H. Dreisbach, M.D., published by the Lange Medical Publishers, Los Altos, Calif., in 1955.

4. The card file systems devised by the Florida Chapter of the American Academy of Pediatrics and the Florida Pediatric Society.

STEP VI.—The sixth step is the preparation of a form for the reporting of the poisoning case. See Chart III for a copy of our form. This form is adequate since it includes the administrative, diagnostic, therapeutic, and follow-up data all on one side of one sheet of paper without duplication. It is mimeographed on eight and one-half by eleven inch paper.

STEP VII.—The final step is to outline the method of operation and staffing of the Center, which will be done by describing a case. The patient is either referred by a physician or comes in of his own volition. He is received by the dispensary clerk, who immediately ushers him to the treatment room. The nurse and the intern on duty in the dispensary then assume charge. The intern proceeds with a cursory history and physical examination related to the poisoning. The reference library is then consulted for toxic ingredient and therapy. Meanwhile, the nurse has prepared the patient for treatment. This entire procedure takes about 5 to 10 minutes, and often less, when the poison and treatment are well known, such as in the case of aspirin. The resident physician is called by the intern for the more serious cases, and the resident, in turn, consults the director when indicated.

While treatment is in progress, the dispensary clerk obtains administrative data from the parents and fills out the dispensary record and the poison control form. When dispensary treatment is finished, the intern completes the professional portion of the form.

If the patient is then sent home, the form is copied and a copy sent to the Child Federation of Atlantic City, a private charitable organization, which cooperates with the Center. If the patient is admitted to the hospital, the form follows the patient upstairs and becomes a part of his chart. After the patient has been discharged, the form is handled as previously mentioned.

CHART III

ATLANTIC CITY HOSPITAL
ATLANTIC CITY, N. J.
POISONING CONTROL PROGRAM

Record No. _____

PART I

To be completed by clerk on all accidental poisonings

Date _____

Name _____ Sex _____ Age _____ Race _____
Address _____ City _____
Name of parent or guardian _____ Phone _____

PART II

To be completed by intern after emergency treatment
If patient admitted, intern on house service completes this part.
(Fill in all blanks or circle correct answer.)

Name of substance swallowed _____ Trade name _____
(Medicine, paint remover, lye, etc.)
Manufacturer _____ Address _____
Amount swallowed _____ Time _____ Date _____
Vomited: Yes or No Time _____ Date _____ Induced: Yes or No
Was stomach lavaged: Yes or No With what? _____
What antidote? _____ How used? _____
Signs and symptoms _____

_____

Disposition of Case: (Circle answer) Sent Home Admitted
Hospital course and treatment _____

_____

_____

Signature _____ M.D.

PART III

To be completed by Child Federation nurse on home follow-up visit

In what room was substance found? _____
Where in room? _____ Is this the usual place? (Circle) Yes or No
Container _____ Who was watching child? _____
Was there a caution on label? (Circle) Yes or No
Was Home follow-up of help in pointing out other accident hazards?
(Circle) Yes or No
Explain _____ In creating opportunities for general Health suggestions (Immunizations, prenatal care, hygiene, etc.) (Circle) Yes or No
Comment _____

Signature _____ R.N.

The home follow-up visit is made by one of the nurses of the Child Federation. Her visit ostensibly is to determine the patient's recovery, but actually to educate the family in accident prevention. This nurse then completes the form, a copy of which is mailed to the State Department of Health for compilation of statistics.

In conclusion, we have found the operation of a poison control center both economical and rewarding. We hope that our efforts will stimulate the development of new poison control

centers and will be of assistance to those already in operation.

ADDENDUM

Since the preparation of this paper, The National Clearing House for Poison Control Centers of the U. S. Public Health Service, has made available duplicate forms for the report of poisonings. By the time of publication, our Center will be using these forms instead of our own less complex version.

Cooperation with the Clearing House is advantageous in that it facilitates the collection of nation-wide statistics.

Excerpts From a Book Review

Christianity in the Kitchen. A Physiological Cook Book. By Mrs. Horace Mann. Boston: Ticknor & Fields. 1858. Pp. 189.

At first the leading title of this book somewhat puzzled us; but, upon a little reflection we decided that, as it is well to carry Christianity into everything in daily life, it is especially needful that the Christian graces be brought to bear in a department of household duty which often involves so much severe trial to the mistress of a family.

We will hazard one or two suggestions semi-critical of portions of the Preface—an important part of this, as it should be of every book. When Mrs. Mann says that "chemical analysis should be the guide for the cookery book," we can only partially endorse the statement. Mainly, it is undoubtedly true; but, in the preparation of food, and still more so in the adaptation of it to the wants of the stomach, and of individual stomach, of very various tone and requirements, chemical rules cannot be over strictly applied. The doctrines of Liebig, at first unhesitatingly accepted, have not obtained that success and verification which was confidently predicated for them. Mrs. Mann quotes from the writings of this justly-distinguished chemist, and more fully from Dr. Johnston's "Chemistry of Life," in most instances judiciously and pertinently. Too many chemical notions, however, should not be administered to people to be swallowed with their food, lest they nervously imagine themselves laboratories, too literally, and precipitate some articles or cause others to combine unpleasantly.

The foundation of Mrs. Mann's receipts—or rather we should say their pervading essence—is CREAM. This is a reform indeed; and we hail with pleasure the successful substitution of an innocent, nutritious article for the *grease* that has so long held its place. The chief difficulty in adopting the author's plan is the expense and the almost impossibility of procuring *real* cream.

We fully endorse the author's proscription of *cream* of tartar, salaeratus, soda, &c., which have been so universally heaped into our food. We have had too much reason to realize the appropriateness of the author's motto on the title-page—"There is death in the pot."

Mrs. Mann must excuse us if we demur at her use of our Savior's words at the last supper, as applicable to our meetings at the "social board." Whilst we agree with her that nothing is more appropriate than to desire and "invite the spiritual presence of Him who said: "Do this in remembrance of Me," we consider that there is a peculiar and sacred restriction of them to the celebration of the ordinance above named, and that they are misplaced elsewhere. With the general tenor of the author's remarks we cordially agree.

BOOK REVIEW IN THE BOSTON MEDICAL AND SURGICAL JOURNAL, MAY 20, 1858.

Clinical Pathological Conference

THE CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

THIS 10-day-old white girl was admitted to The Children's Medical Center for the first time with a diagnosis of ruptured spleen. The child was the second-born of twin girls, the product of a normal full-term pregnancy and delivery. She weighed 5 pounds, 8 ounces at birth, but did not thrive like her sibling. Thirty-six hours prior to admission the child was noted to be pale and to have a distended abdomen.

Shortly after admission the infant was explored, and a ruptured spleen was removed. Postoperatively, the child vomited excessively, gained weight poorly, and was lethargic. Roentgenograms revealed a partial obstruction of the intestine; this responded well to suction. A urinalysis now revealed a pH of 5.5, a specific gravity of 1.010, albumin 100 mg. per cent, and many erythrocytes and leukocytes per high-power field in the urine sediment. The serum nonprotein nitrogen was 81.9 mg. per cent. After a period of several days on antibiotics and supplementary intravenous fluids, it was 57.3 mg. per cent. Because of the continued nitrogen retention, the infant was transferred to the medical service at 1 month of age.

At the time of transfer, the vital signs were normal; the weight was 12 ounces under the birth weight. The infant was poorly nourished, but, except for a well-healed abdominal incision, the physical examination was negative. The hemoglobin then was 15.6 Gm. per cent; the leukocytes numbered 10.1 thousand per cubic millimeter. The urine pH was 5.5, specific gravity 1.014, and was negative for albumin and sugar; the sediment contained occasional erythrocytes, leukocytes, yeasts, bacteria, and epithelial cells. The serum Hinton reaction was negative. The serum nonprotein nitrogen was 87.4 mg. per cent. The nose and throat cultures grew a few colonies of *Staphylococcus aureus* and *E. coli*.

The infant was offered a high-caloric diet, but gained weight slowly. Two weeks after transfer, the nonprotein nitrogen was still high, the urine specific gravity low, the sediment now contained granular and hyaline casts, as well as erythrocytes and leukocytes. The urine culture was sterile. The penicillin and streptomycin were replaced by chloramphenicol. Over the next two weeks the nonprotein nitrogen fell from 90.6 to 35, the serum phosphorus from 12.1 to 6.5 mg. per

cent, and the hemoglobin to 9.5 Gm. per cent, while the carbon dioxide content rose from 15.8 to 21.8 mEq. per liter, the reticulocytes from 0.6 to 0.4 per cent, the calcium to 11.3 mg. per cent, and the child's weight to 6 pounds, 5 ounces.

Six weeks after entry, further x-ray studies were carried out. A cystogram and voiding urethrogram were normal. Intravenous pyelograms, after two hours, outlined the upper respiratory tract poorly, but dilatation of calyces and valves was thought to be present.

Eight weeks after entry a harsh grade II systolic murmur was heard at the left sternal border. The electrocardiogram was normal; the cardiac silhouette was slightly but nonspecifically increased in size. Over the next two weeks, the infant had occasional sharp transitory elevations in temperature. The urine during this period contained albumin—from a trace to 2 plus, and 5 to 10 leukocytes were present; one urine culture was positive for *B. proteus*. The nonprotein nitrogen fell further to 20, the phosphorus to 5.2, and the calcium to 10.9 mg. per cent. The hemoglobin fell further to 6.5 Gm. per cent, though the reticulocytes remained elevated. Repeat pyelograms two weeks later outlined the right kidney very faintly and the left not at all; a nodular mass was felt in the latter region. Retrograde pyelograms outlined a slightly enlarged left kidney with a normal pelvic and calyceal outline. The urine now had a specific gravity of 1.014, with 3 to 5 leukocytes in the sediment.

The infant, weighing 7 pounds, 1 ounce, was discharged from the hospital after a stay of two and a half months, on sulfadiazine. She initially did well as an outpatient, but then developed fever and anorexia, with a nonprotein nitrogen of 40 mg. per cent. The urine again contained albumin (1 plus), erythrocytes 10 to 20, leukocytes 1 to 2, and occasional granular casts per high-power field. Because of these findings and an elevated blood pressure, periorbital edema, and an enlarged liver, she was again admitted, two and a half weeks after discharge.

On re-entry, the temperature was 99.4° F., the pulse rate 130 per minute, the respirations 36 per minute, and the blood pressure 125 mm. Hg systolic, and 80 mm. diastolic. The weight was 9 pounds, 2 ounces. The infant was well developed and well nourished. There was edema of the feet. The heart was slightly enlarged. The pulmonary second sound was louder than the aortic; a grade II to III systolic murmur was present at the left sternal border. The liver was palpable 4.0 cm. below the costal margin. A hard mass, 3 to 4 cm. in diameter, thought to be kidney, was palpable in the left upper quadrant.

The urine was unchanged, though cultures grew out *E. coli* and *B. proteus* organisms. The peripheral leukocytes numbered 30.9 thousand per cubic millimeter, with a differential count of polymorphonuclears 40, basophils 8, lymphocytes 48, and monocytes 4 per cent, with 10 nucleated red cells per 100 leukocytes. The platelets appeared to be normal in number. The serum chemistries were: pH 7.2, carbon dioxide content 20, sodium 150, potassium chloride 10.9 mEq. per liter, nonprotein nitrogen 41.5, calcium 10, and phosphorus 7.4 mg. per cent. The blood culture was sterile. The nose

and throat cultures grew a few *C. coli*, *B. proteus*, and *Staph. aureus*. The electrocardiogram suggested combined ventricular hypertrophy. The heart, by roentgenograms, appeared enlarged, with left ventricular predominance. A flat film of the abdomen showed a slightly enlarged liver and increase in both renal shadows.

The child was again placed on chloramphenicol. The peripheral edema and the enlarged liver were no longer evident, though her blood pressure remained elevated and spikes of elevated temperature recurred. Retrograde pyelograms again demonstrated increased size of kidneys with reflux of the dye into the collecting tubular system, outlining minute calyceal cysts or dilatation of the calyces. Split renal function studies gave the following results.

	Right	*Left*
Glomerular filtration rate (ml./min.)	3.6	0.9
Renal plasma flow (ml./min.)	11.2	3.2
Filtration fraction	0.23	0.28

The blood pressure decreased slightly, and on the thirteenth hospital day an operation was performed.

DISCUSSION

DR. WARREN R. GUILD.*—First of all, this is a 10-day-old girl who had ruptured her spleen. Why has she ruptured her spleen? That is not at all clear. Undoubtedly, my guess would be that this was not because of a traumatic delivery since she went on for ten days in relatively good shape. Characteristic of her clinical course is the fact that she had continued sepsis, though it was of a low-grade variety, just as was the degree of her uremia and her acidosis.

Her urine, from the time of first observation, was very abnormal. The specific gravity tended to be constantly low, as did the pH. She had an intermittent albuminuria but with continuous loss of erythrocytes and leukocytes, but with few casts. She was uremic on the first admission to the hospital. Two things were interesting about her urine. First of all, bacteria were observed in the sediment, but in the absence of a positive urine culture. I think I would interpret this to mean that the bacteria found in the sediment were a result of standing, or possibly the bacteria involved were of such an exotic nature that they would not be picked up on routine culture. In any event, these data do not help the diagnosis I am going to make. She already had a nonprotein nitrogen at a uremic level. On the basis of the urinalysis she was started on Chloromycetin, so it was felt by her physicians that there must have been a significant bacilluria. No mention is made of the presence or absence of oval fat bodies, which would be helpful in the diagnosis of nephrotic syndrome.

Why is the patient anemic? I think there are two reasons: first, infection must play a part because she developed a reticulocytosis when the infection was brought under partial control, and second, her uremic state plays a definite role in her anemia.

Did this patient, at any time in the hospital, have a cholesterol and a total protein drawn? An intravenous pyelogram showed the faintest suggestion of an outline of the upper urinary

*Dr. Guild is Instructor in Medicine, Harvard Medical School, and Associate Director of the Cardio-renal Laboratory at the Peter Bent Brigham Hospital.

tract; this fact speaks strongly, of course, for grossly impaired glomerular filtration.

During her hospital course she developed a grade II harsh systolic murmur in the absence of cardiomegaly. The word here that bothers me is "harsh." I would have been happy to ascribe this murmur to anemia, if the word "harsh" were not there, but I think I will consider this as a hemic murmur anyway.

She now begins to develop involvement of organs other than the kidneys.

On the second admission, retrograde pyelograms showed an increased size of both kidneys. Either the involvement is now bilateral, or the initial damage may have been to the left kidney which had a grossly abnormal glomerular filtration rate and renal plasma flow. The right kidney has undergone compensatory hypertrophy. This may well be possible, but a disturbing feature here is that the compensatory hypertrophy is only anatomical and not functional, since the function of the right kidney is also below normal, although not as bad as that of the left kidney.

May we see those x-rays now?

DR. CRAIG.—Dr. Farber, may I supply one bit of information which was not in the chart, which may be important? On the first admission the child was in severe shock after the rupture of the spleen.

DR. MARTIN H. WITTENBORG.—The initial films of the abdomen, prior to the removal of the spleen, show gross distention of the abdomen with a diffuse homogeneity and no gaseous distention of the small bowel; all this suggests free fluid in the abdomen.

After the operation, the right kidney shadow is possibly enlarged; the left is not. There is so little concentration of dye on the intravenous pyelogram that visualization of the upper urinary tract on the left was not possible, but in later films calyces on the right side were faintly outlined and dilated, but there was no gross distortion. The retrograde pyelogram on the right shows a spread of the calyceal pattern, suggesting a diffuse enlargement of the kidney. The pelvis was large, but the outline does not suggest an obstructive type of dilatation.

On the retrograde pyelograms, done on the second admission, we have an enlargement of the whole drainage system. There is considerable distortion of the calyces with some sort of an odd type of reflux into the kidney parenchyma.

DR. GUILD.—How much of this do you think could be due to overdistention of the calyces by increased pressure of injection of the dye?

DR. WITTENBORG.—That is very difficult to evaluate because here is a pressure-sensitive membranous type of structure; with a little increase in pressure the calyces will balloon out. They also had a similar configuration on the intravenous urogram. We thought it was probably a definite anatomic anomaly. We commonly use the term "calicalectasis" for a mild dilatation of a nonobstructive type. This nodularity of outline of the kidney is probably related to the fetal lobulation, rather than a localized mass.

DR. CRAIG.—Dr. Farber, may I ask Dr. Wittenborg if he sees any suggestive so-called "ring," or "sling sign"?

DR. WITTENBORG.—We don't see that in this case.

DR. GUILD.—The differential diagnosis, I believe, may be found within five separate entities.

First, I think renal obstruction must be considered, but now that we have seen the pyelograms, I will just dismiss that. Second, metastatic infection or local infection is a possibility on the basis of the septic course; that the patient had a harsh murmur with cardiomegaly indicates a possibility of bacterial endocarditis with particular seeding of the liver and kidneys. Against such a diagnosis are the facts that the patient was unresponsive to adequate doses of penicillin, streptomycin, chloromycetin, and sulfa, and the blood and urine cultures were negative. I think that infection as a primary event is probably very unlikely. A third possibility (and I base this on the fever, the evanescent leukocytosis, the multiple organ involvement of the spleen, the liver, the kidney, and the heart) is that of hypersensitivity angiitis. I would not attempt to make a differential diagnosis between lupus or periarteritis. I would just call it hypersensitivity angiitis. I don't think that this was due to the drugs because the renal failure antedates the infection. I can't understand why an operation would be performed on a patient with hypersensitivity angiitis, nor can I understand why there would be a left upper quadrant mass. A fourth possibility, which perhaps is the best (but I hope the wrong diagnosis) is polycystic disease of the kidney or the kidneys. I doubt that, first of all because at the time of splenectomy I hope the left kidney was looked at, and this diagnosis thus might have been suspected; the retrograde pyelograms are hardly suggestive, and this would not explain, to my mind, a left upper quadrant renal mass, nor would it explain why an operation would be performed—unless this was a large infected cyst. Again, the x-rays help us to rule that out.

Lastly, as my best diagnosis, I consider this case to be one of renal vein thrombosis. I am going to make a distinction between that and renal arterial occlusion. Why could this patient have renal vein thrombosis? First of all, there was a good chance that the blood was hypercoagulable due to hyperthrombocytopenia just after the splenectomy. Second, this patient is in the ideal age range—less than 1 year old (as a matter of fact, less than 1 month old when she first became ill). She had a septic course with many leukocytes in her urine. Third, she was dehydrated, secondary to her vomiting. She had, initially, unilateral involvement and I have tried to explain the fact that there was bilateral enlargement on the basis of hypertrophy of function of the uninvolved kidney. She had hematuria, pyuria, and albuminuria, with negative urine cultures. She had no excretion of dye from the left kidney on the initial intravenous pyelogram, yet normal retrograde pyelograms. There are several points against renal vein thrombosis, however—first of all, the evanescent downhill course. She was very ill early in life, yet subsequently she thrived, was well developed and well nourished, and had a normal serum nonprotein nitrogen. I would feel more certain of my diagnosis if this course were more inexorably and relentlessly downhill. She had hepatomegaly and splenomegaly, and that is

very hard to understand. She did not have the nephrotic syndrome as a part of her illness, and I take that to indicate that the involvement was unilateral rather than bilateral. In experimental animals one can produce nephrosis on the basis of unilateral renal vein thrombosis, but it is hard to find a case which is well documented in either the pediatric or the medical literature.

Why is this not renal arterial occlusion, as would be suggested by the leukocytosis, the albuminuria, and the impairment of concentration ability? First of all, the kidneys were enlarged (which is against this) and this went on for three to four months. The course was septic. Classically, the patients who develop renal arterial disease occlusion have an aseptic course, a very good prognosis, and the kidneys become small. They also have preexisting cardiovascular disease. There was no suggestion of cardiovascular disease in this patient until her kidneys began to fail. An aortogram was not done, I believe.

My final diagnosis, therefore, is hemorrhagic infarction of the left kidney on the basis of renal venous disease, presumably renal vein thrombosis.

DR. FARBER.—Dr. Schwartz, would you like to speak at this time?

DR. ROBERT SCHWARTZ.—Dr. Jack Metcoff saw this patient on many occasions, and I will attempt to speak for him, to the best of my ability. He was impressed with the same features as Dr. Guild.

I just want to mention the renal function studies since Dr. Guild did not go into these in detail. These values are given in cubic centimeters per minute, and are not corrected on the basis of square meterage. The surface area was 0.24 meters square—for those who want to apply the correction. Comparing the two sides, the left had 0.9 compared to the right, with 3.6 c.c. per minute for glomerular filtration, and 3.2 compared to 11.2 c.c. per minute for renal plasma flow. On the left, then, both glomerular filtration and renal plasma flow were reduced. The filtration fraction is identical with the right, which could be interpreted as meaning that these nephrons were functioning in a reasonably normal fashion. The difficulty in interpreting this will become apparent from Dr. Metcoff's note. The problem here is that the left values are grossly abnormal—but is the right abnormal, also, and does an easily demonstrable abnormality on the left contribute to the diagnosis? The problem is that, in dealing with an infant 4 months of age, renal function is very "immature," and glomerular filtration values do not reach normal levels until somewhere between 4 and 6 months. This baby is in the borderline group where glomerular filtration is still a little bit low normally, and the same thing is true of renal plasma flow. Thus, one cannot give a definitive opinion regarding the right side. At 4 months, Dr. Bruck's data (1) show a filtration rate of 40 c.c. per square meter, compared to values on an older child of 60 to 80 c.c. If you take half of 40, you are down to 20 for one kidney, and for this child the values are about 12 or 14. The difference is between values of 12 and 20. To say that this is a definitively abnormal value, I think, is difficult.

Dr. Metcoff's comments were: "The history and course of this child suggested a unilateral vascular renal lesion, probably associated with a traumatic birth. . . . The clearance value suggests about 65 per cent reduction of the glomerular bed, and 72 per cent reduction of the renal plasma flow in the left kidney when compared to values obtained from the right kidney. At catheterization, urine from the left ureter was bloody, that from the right was clear. However, this could have been due to the operative manipulation and may have no significance. I believe the clearance data are suggestive and compatible with subcortical renal hemorrhage, with probable infarction of two-thirds of the left kidney. I would suggest that the patient have a left renal exploration and possible excision of this kidney."

This difficulty of interpretation then with this child was noted by Dr. Guild when he wondered whether the left side was abnormal, and whether the right side represents so-called compensatory hypertrophy in a normal right kidney.

Could the increase in susceptibility to infection in a splenectomized infant raise the question of whether sepsis and pyelonephritis might not have been underlying the entire course here?

DR. FARBER.—Thank you very much, Dr. Schwartz.

DR. CRAIG.—Dr. Metcoff, preoperatively, did not think that pyelonephritis was a very important part of this picture.

DR. LUTHER A. LONGINO.—We did not have any history of a breech delivery or of any trauma at the time of birth in this child which might lead to the ruptured spleen. We have seen children with ruptured spleens and also ruptured kidneys after breech deliveries. Whether or not the renal lesion in this case was associated with the same injury which caused the splenic rupture, I don't know.

The operative procedure was straightforward. The operative note says that both Dr. Craig and Dr. Metcoff discussed the problem at length after the frozen section, but the nature of their discussion was not recorded.

DR. FARBER.—Dr. Diamond, would you like to add anything at this time?

DR. LOUIS K. DIAMOND.—A good survey by Dr. Philipsborn[2] in Montreal, of cases of ruptured spleen in the newborn, shows that every one of them had been subjected to some form of trauma, either by breech delivery with hard pull on the pelvis, or by resuscitative measures with the child being doubled up and stretched out many times—so the ribs could have been pressed into the spleen. Dr. Philipsborn points out that many of these patients did not have symptoms immediately. They often had a subcapsular hemorrhage which continued to ooze slowly and then, suddenly, either ruptured, or enough blood was lost, so that they went into shock the second, third, or fourth day—rather than on the first day as you would expect with an immediate tear in the capsule. As to the question of sudden, severe overwhelming infections in this age group after splenectomy, the figures show a small but definite hazard in that respect in children under 2 years of age.

DR. CRAIG.—After Dr. Longino's remarks, maybe I should not have

brought this case up. However, I will say that at the time of operation, first a small biopsy was done on the cortex, and then frozen sections were examined. Dr. Metcoff and I sat down and tried to figure out what was actually wrong with the kidney, and what should be done for this child. We saw, in the frozen sections, a marked dilatation of many of the tubules, and many of the Bowman's spaces. On the basis of this finding, we thought that this might represent a case of unilateral cystic disease of the kidney. We did not see much evidence of infection on the frozen section, but some of the small vessels were sclerotic and this was quite in keeping with the child's hypertension.

The most striking feature of the removed whole kidney is the loss of the tips of all the renal papillae (Fig. 1). These are blunted and replaced by dense scar tissue, aligned parallel to the surface. The pelvic epithelium is regenerative (Fig. 2). There are remnants of inflammatory cells here and in the adjacent pelvic submucosa. Locally, on the cortex, there is dilatation of Bowman's space and the proximal tubules, with a few casts which stain for uric acid. There were foci of chronic pyelonephritis with interstitial inflammation and tubular atrophy (Fig. 3). The arteriosclerosis was not marked in this child.

We considered this case, then, one of healed papillary necrosis, with some pyelonephritis superimposed. I believe that the child, even on her first admission, had a few white cells. She had one urine examination in which there were white cell casts. I wonder whether the combination of the shock that this child had, plus her pyelonephritis, had not induced this lesion.

The problem of papillary necrosis in adults is quite well defined. There have been large series of papers on this lesion, with nearly 160 cases reported in the literature. Ninety of these 160 occurred in patients with diabetes.[3, 4] Between 3 and 5 per cent of all autopsies of diabetic patients have papillary necrosis, and this is against 0.7 per cent of all other nondiabetic patients. Pyelonephritis is very common in any series of autopsies and often patients running up to 20 per cent among those diabetics having pyelonephritis, nearly 30 per cent have papillary necrosis. This, then, is a very close relationship between pyelitis, pyelonephritis, papillary necrosis, and diabetes. These figures are in contrast to the 2 per cent of nondiabetics who have pyelonephritis at autopsy with papillary necrosis. Most of the diabetic patients do not have unilateral obstruction. The ratio is 5 to 1 against there being obstruction in patients with diabetes and papillary necrosis, against a ratio of 3 to 1 for there being obstruction in the nondiabetics. Cases are reported in which there is healing of the unilateral process when the affected kidney has been removed.

The problem is more obscure in children, I think. I could find only one case in the literature in which there is evidence of papillary necrosis.[5]

Two other cases have been seen in our hospital. The first was in a child who was on the beach, developed a temperature of 105° F., became comatose, and had all the typical changes of heat stroke plus the renal papillary ischemic necrosis in a very early stage. The second child also had a history of hyperthermia and had an identical lesion of the kidney.

Fig. 1.

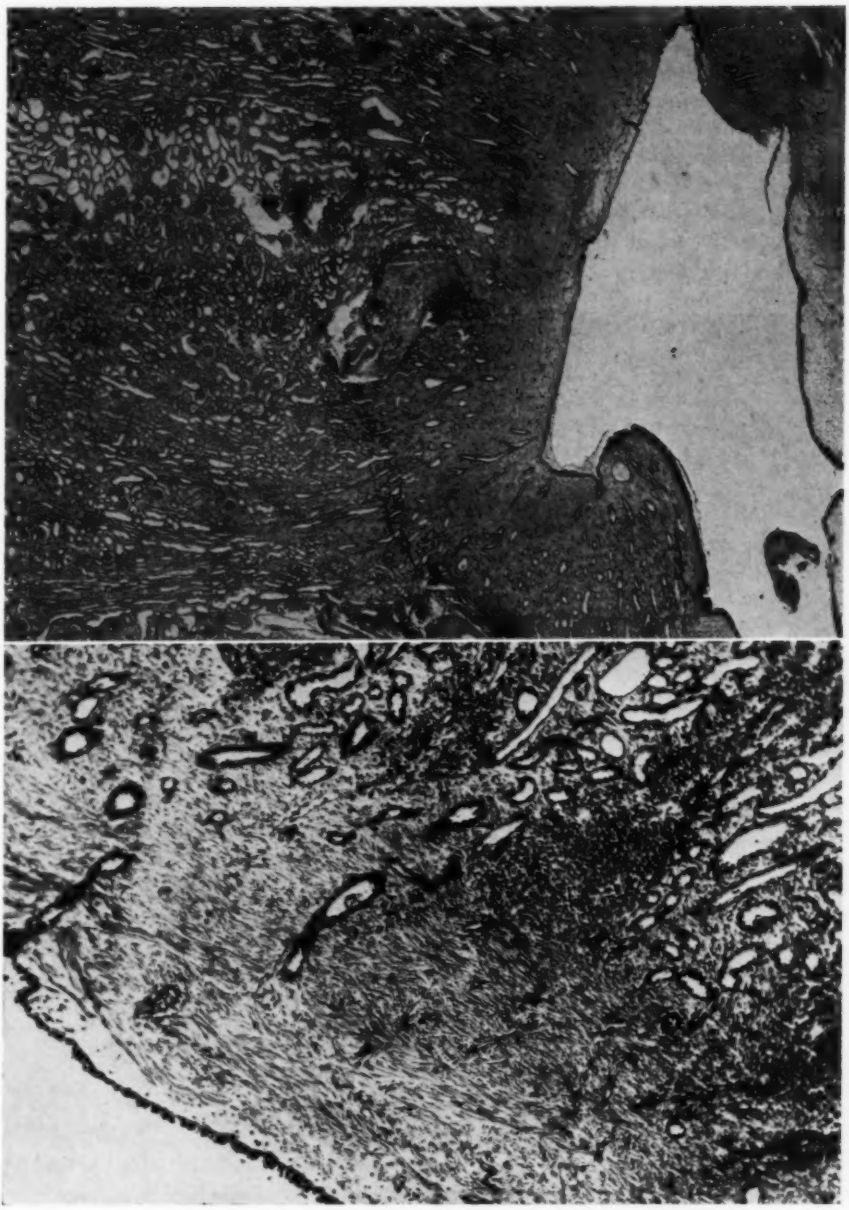

Fig. 2.

Fig. 1.—Photomicrograph of kidney. The papillae has lost its tip, and the truncated papillary cone has been replaced by scar tissue. (Toluidine-blue-eosin, ×25.)

Fig. 2.—Photomicrograph of kidney. The scarring of the papilla and submucosa and the inflammation are evident. (Toluidine-blue-eosin; ×100.)

The etiology of these papillary necroses is not well understood. No one single etiology is recognized. There have been suggestions of poor blood supply, compromised by vascular disease, compression of the medullary vessels associated with infection, with contraction due to scar, or spasm of the contractive smooth muscle elements in the papillae which shut off the blood supply and induce ischemia.

tion in the cortex. The second general method of inducing this lesion is by tying the ureters and injecting bacteria into the blood stream.

One of the functional results in the experimental rabbit[6] is a hyposthenuria, seen also in this patient.

Whether we were justified in removing this kidney, I think, is perhaps partially answered by the subsequent course of the child.

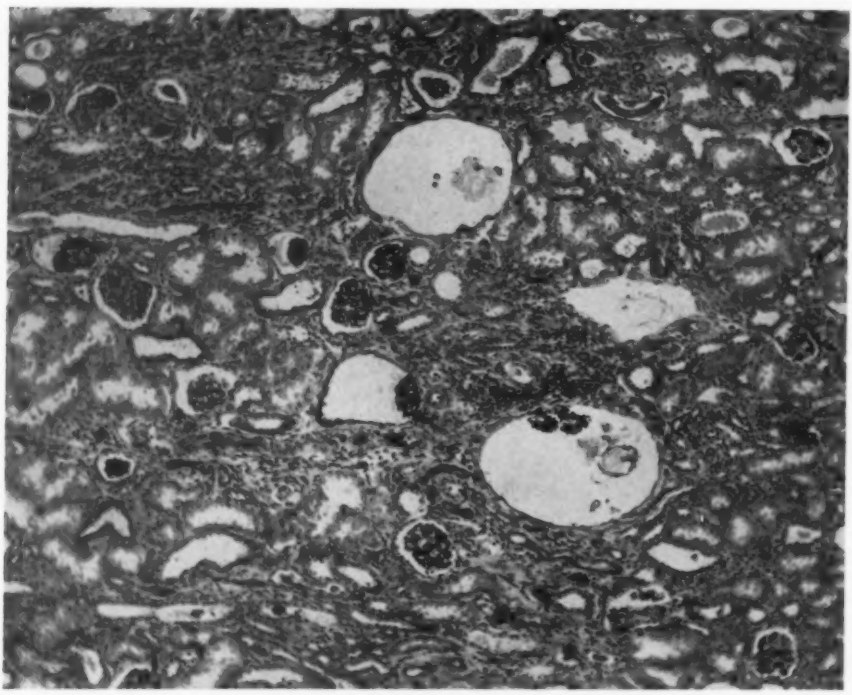

Fig. 3.—Photomicrograph of kidney. A small focus of pyelonephritis is present in the cortex. Many Bowman's spaces and proximal tubules are dilated. (Toluidine-blue-eosin; ×100.)

Experimentally, there are two methods of producing this lesion. One is the injection of nephrotoxic agents—which include vinylamine, tetrahydroquinoline, and mono-methyl-aniline. In rats, diets lacking in fat will induce papillary necrosis, along with calcifica-

DR. WITTENBORG.—What was the size of this kidney?

DR. CRAIG.—This child's kidney weighed 20 grams, which is essentially normal for this age. The pelves, in general, were not enlarged, except in

the region of the calyx, where loss of tissue had increased its size.

DR. WITTENBORG.—Did these dilated tubules and Bowman's spaces reach macroscopic size?

DR. CRAIG.—No, they did not. It is an obstructive lesion, and this has also been recognized in experimental animals.

DR. FARBER.—May we have a word now on the subsequent course?

DR. WILLIAM LONDON.—This child has been admitted here twice since that time. The first admission was for an acute gastroenteritis, and at this time her blood pressure was recorded as 130/90 on several occasions. Urinalysis at that time showed a specific gravity which varied from 1.008 to 1.018 and her serum nonprotein nitrogen ranged around 30 to 40 mg. per cent. She was readmitted again and at this time her nonprotein nitrogen was 38 mg. per cent. Her blood pressure varied at this time; sometimes it was hypertensive and at others normotensive. Urinalysis at this time continued to show white cells and culture revealed *B. subtilis*. Her urine sediment has been consistently negative, with no cellular elements. We have done methylene blue stains for bacteria and have not seen any bacteria, but the most recent cultures have grown out a *B. proteus*, which are sensitive only to chloramphenicol and neomycin. Her right kidney seems to be enlarged. The remainder of the physical examination is normal.

DR. FARBER.—Dr. Wittenborg, would you show the repeat pyelograms?

DR. WITTENBORG.—Again we get the impression of a wider spread of the calyceal system than is normal, but I do think the concentration of dye is better, and she does have a good concentration of dye in the bladder.

DR. FARBER.—Dr. Guild, would you like to make concluding remarks?

DR. GUILD.—Because of the fact that this child had no diabetes, and because she was so young, I dismissed papillary necrosis.

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Medical Progress

RECENT ADVANCES IN GENETICS IN RELATION TO PEDIATRICS

F. Clarke Fraser, Ph.D., M.D.
Montreal, Canada

EXCITING things have been happening in genetics in the past few years, many of them directly or potentially relevant to the practice of medicine. This article will not attempt to review all the voluminous literature on gene form, function, and frequency,[63, 192] or even all the recent developments in human genetics,[21, 154] but will discuss some of the current trends in genetics and their clinical implications.

I. Nature and Action of the Gene

Through the exploitation of new biochemical techniques in a host of organisms ranging from microbes to man, a great deal is being discovered about the intimate structure of genes and about their behavior in cells, organisms, and populations. No longer can the gene be considered a bead on the chromosomal string, responsible, in some magical way, for a particular trait of the organism. Rather we may think of a specific biochemical function[152] associated with a particular region of the chromosome, dynamically related to adjacent regions of the chromosome and to the surrounding cytoplasm. Like the "indivisible" atom, the gene is now separable into several component parts, and it has even been suggested that the word "gene" should be replaced by other terms (muton, cistron, and recon)[18] depending on what aspect of it is being considered at the time. Nevertheless, in medical genetics the word "gene" should be useful for some time yet.

A. *Gene Structure.*—There is now a great deal of evidence to suggest that the specificity of the genetic material lies in the particular arrangement of nucleotides in the double-helical strands of desoxyribosenucleic acid (DNA) that, along with the protein backbone, make up the chromosomes.[34, 193] Outstanding among the lines of evidence pointing to DNA as the carrier of genetic information is the demonstration that the genetic structure of a pneumococcus, for example, can be changed in a regular and predictable way by exposure to DNA from a genetically different pneumococcus. This change can be effected through direct exposure to the DNA (transformation)[178] or by transfer of DNA from one bacterial cell to another by bacteriophage (transduction).[110] This subversion of the concept of gene constancy has

From the Departments of Genetics and Paediatrics, McGill University, and the Department of Medical Genetics, The Montreal Children's Hospital.

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been clearly established in several species of microorganism, but except for one yet-to-be-confirmed report involving (of all things) beak color in ducks,[9] there have been no instances so far of DNA-induced transformations in multicellular organisms. The possibility that such things could be done in human beings has many intriguing and some alarming implications.

Another attack on the Mendelian concept of the inviolacy of the gene has been made in plants where Brink has shown that in corn, combination of a particular pair of genes affecting aleurone color always leads at meiosis to a change in the genetic nature of one of them.[23] Similar processes may occur in Neurospora[27, 127] and yeasts,[112] though not so regularly.

Still more upsetting to orthodox genetic theory is the recent discovery of genetic entities that can move about from chromosome to chromosome and affect the behavior of the genes in the region in which they happen to be at the time.[116] This extraordinary situation (which has so far been found only in plants) may have important implications for the central problem of differentiation—i.e., why cells which are (supposedly) identical genetically, follow different developmental paths.

Also relevant to the problem of differentiation are the studies of Puck[156] who has developed a method of growing pure clones of mammalian somatic cells by techniques comparable to those of bacteriology, thus getting rid of the difficulty due to fibroblasts overgrowing other cell types in ordinary tissue cultures. This technique should open many new avenues of genetic, embryological, and biochemical knowledge. It can profitably be applied, for instance, to the study of biochemical mutants in man, carcinogenesis, embryonic differentiation, and sensitivity of human cells to radiation. Puck has shown, for example, that, within a human cancer cell strain, different cells may have different growth requirements.[155] Clearly, the assumption that the morphologically similar cells of a tissue are also functionally similar is unjustified. Koller[106] and others have also emphasized the genetical heterogeneity of tumor cell populations and have shown how the characteristics of a neoplasm may alter according to the pressures of mutation, selection, and adaptation—findings important to those working in the field of cancer therapy, for instance.

In an elegant series of experiments, King and Briggs[102] have shown that this sort of heterogeneity of cells within a tissue exists also in the frog embryo, and that here the heterogeneity is nuclear in origin. When individual nuclei from the cells of a late gastrula are transplanted to enucleated eggs, some eggs will complete development and others will cease development at one stage or another. Thus within the same somatic tissue, some nuclei are just as capable of maintaining development as the original egg nucleus, but others are limited in their developmental potentialities—i.e., they have become differentiated. Serial nuclear transplantation experiments have demonstrated that the degree of nuclear differentiation possessed by each gastrula nucleus is transmitted to its descendants. It would seem that one cannot think of differentiation simply in terms of

genetically identical nuclei acting on differing cytoplasms. The nucleus and cytoplasm are a constantly interacting system, and similar nuclei, that build their constituents from different cytoplasms, may themselves become different.

B. *Gene Function.*—Great advances have also been made in our knowledge of gene function. According to one modern concept, the genetic information, transmitted from generation to generation in the DNA, is transferred in the somatic cells to the RNA (ribosenucleic acid), from whence the genetic specificities are imprinted on the macromolecules being synthesized in the cytoplasm.[31] The idea developed mainly from the work of Beadle[16] and others on the bread mold, Neurospora, where the close correspondence between a mutant gene and a specific step in a particular biochemical process led to the formulation of the "one gene–one enzyme" hypothesis, this was later extended to proteins other than enzymes.[187] Though the hypothesis may be an oversimplification of the facts, it has been an extremely productive one.

By the use of mutants that "block" specific metabolic steps a great deal has been found out about the cell's metabolic pathways, not only in microorganisms, but in humans.[31] In some microorganisms it is even possible to show that successive steps in the synthesis of a molecule, such as tryptophane, are made by a series of closely linked genes, arranged along the chromosome in such a way that the sequence of genes corresponds to the sequence of synthetic steps, as if the molecule being synthesized were being passed from one gene to the next in production-line fashion.[38] This does not seem to occur in the higher organisms, however.

Studies on many organisms, including viruses, bacteria, fungi, Drosophila, and humans, have provided a great deal of evidence that the primary function of a gene is to imprint its specificity on a macromolecule such as an enzyme, antigen, or hemoglobin. Alteration of a gene, therefore, causes an alteration in specificity of the macromolecule concerned, and this may alter, more or less profoundly, the characteristics of the organism. This hypothesis has led to the concept of "molecular diseases"[143] (see section V, E, 2, on the abnormal hemoglobins), has enhanced our knowledge of the "inborn errors," and has led to an important medical application of genetics, namely, detecting genetic carriers of inherited diseases (see section V, C).

II. DEVELOPMENTAL GENETICS

A. *Teratogenic Genes.*—In the rapidly growing field of mammalian teratology genetic studies have made important contributions to knowledge. In mammals one cannot operate satisfactorily on the developing embryo, but one can make use of naturally occurring "operations," performed by mutant genes with very specific effects on certain embryonic stages, and study the mechanisms by which these developmental errors give rise to malformations. For example, embryological analysis of the "Sd" gene, which produces malformations of the genitourinary system and tail in the mouse, has shown that kidney aplasia or hypoplasia is, in this case, a result of inhibition of growth of the ureter, and

implies that normal metanephric development depends on an inductive stimulus from the ureteric bud.[73]

Gluecksohn-Waelsch[66] has recently discussed a number of mutant genes affecting development of the central nervous system. One group have provided evidence to suggest that an inductive relationship between notochord and neural tube exists in the mouse as it does in the Amphibia. Other mutant genes affect closure of the neural tube, and others involve individual regions of the central nervous system at later stages of development. For instance, the recessive mutant gene "eyeless" in the mouse acts by retarding growth of the eye vesicle, and delaying its approach to the overlying ectoderm, with consequent failure of lens induction and a variety of secondary abnormalities. Thus a mutant gene has been used to show that the formation of a normal lens appears to depend on an inductive stimulus from the optic vesicle.

Embryological studies on hereditary hydrocephalus in the mouse have traced at least two developmental pathways by which this anomaly can occur. In one type, shortening of the basicranial cartilage leads to dorsal bulging of the cerebral hemispheres, telescoping of the lower parts of the brain, failure of formation of the foramen of Magendie, and development of a "classical" obstructive hydrocephalus.[74] In a genetically different form, the defect apparently begins with an abnormal transudation of fluid from the columnar epithelium of the neural tube. Later, when the choroid plexus forms, the fluid is directed into the ventricular system, which thereupon dilates, except in the region of the relatively resistant posterior commissure. Consequent distortion may lead to obstruction of the aqueduct, and exacerbate the hydrocephalus.[21] Examples such as this demonstrate, in a manner impossible to achieve in humans, how *different developmental errors may lead to the same clinical end result.*

Conversely, the same developmental error may lead to a variety of end results which, without developmental analysis, may appear to be totally unrelated. Gruneberg,[71] for instance, has demonstrated a "pedigree of causes" in a rat mutant where such diversified things as emphysema, and right heart failure, faulty occlusion of the incisor teeth, kyphosis, and narrowing of the tracheal airway can all be traced back to a defect in cartilage formation. This and other examples illustrate how widespread the secondary effects of a specific gene-determined abnormality can be, and how greatly *the individual features of a genetic "syndrome" can vary from individual to individual.* Such analyses will no doubt reveal many hitherto unsuspected developmental relations. A particularly striking example is the recessive "Disorganization" gene in the mouse[86] that appears to have widespread disruptive effects on development, so that affected young may have one or more of a fantastic array of defects including exencephaly, spina bifida, gastroschisis, anophthalmia, cleft palate, kidney and gonad agenesis, duplication of limbs, tongue, or intestine, and many others. Further analysis of this unusual situation should be of great interest, both to embryologists and to physicians.

McKusick[121] shows how the principles of developmental genetics can be

extended to clinical examples such as Marfan's syndrome, where a "pedigree of causes" can be postulated, tracing from the effect of the gene on connective tissue to the widespread and variable features of the syndrome, each feature being susceptible to alteration by secondary environmental or genetic modifiers. The elongation of the fingers, for instance, may be completely suppressed if the gene is imposed on a "pyknic" constitution. On the other hand, the degree of physical stress imposed by the environment may determine whether the genetically predisposed aorta will develop a dissecting aneurysm. In his book, *Animal Genetics and Medicine*, Gruneberg[73] points out many other opportunities to gain clinically relevant information from embryological analysis of genetic material in the lower mammals.

B. *Other Teratogenic Agents.*—Recently the field of experimental teratology has been greatly stimulated by the realization, due largely to the outstanding studies of Warkany,[190] that although one cannot operate successfully on a mammalian embryo, one can alter its development in rather specific ways, by subjecting it to biochemical insults such as maternal vitamin deficiencies or physical hazards such as radiation.

Here again, awareness of genetic principles has been useful. For one thing, the fact that there are differences in the ways genetically different animals react to the same environmental stimulus accounts for many of the discrepancies between the results of different workers performing the same experiment. For instance, it reasonably accounts for the fact that Andersen[4] induced diaphragmatic hernias in the offspring of vitamin-A-deficient rats whereas Warkany,[191] using another strain, did not. Where species differences are concerned one would expect much greater discrepancies in reactions to the same agents. This should remind us that the results of experiments in lower mammals do not necessarily apply to humans—they may suggest what features to look for in human teratological studies, but the final proof that a given agent is teratogenic in humans must depend on clinical data.

Marked differences in the reactions of different inbred mouse strains to the same teratogenic agent have been demonstrated in the case of maternal fasting,[128] galactoflavin,[99] and cortisone.[58] In the latter case genetic analysis has provided evidence that both maternal and fetal genotypes are involved, and that in strains susceptible to the cleft-palate-producing properties of cortisone the palate normally closes later than in resistant strains. This has led to investigation of the force that makes the embryonic palatine shelves approach each other against the resistance of the tongue. A better understanding of the physical basis for resistance to teratogenic agents might have useful clinical implications.

III. CYTOGENETICS

A. *Human Chromosome Number and Morphology.*—New impetus has been given to the study of human chromosomes by the development of improved techniques of observation[85] and the consequent discovery that the normal diploid chromosome number in man may be forty-six, rather than

forty-eight.[51] It may be, in fact, that both counts are correct, some individuals having forty-six and some forty-eight.[105]

The cytological approach may also prove useful in studying the genetic effects of radiation in humans by measuring the sensitivity of human chromosomes to radiation-induced breakage (preliminary studies suggest that they may be more sensitive than previously suspected[17]) and in eventually providing chromosome "maps"[166, 199] whereby specific mutations might eventually be assigned to specific cytological loci.

B. *Determination of the "Chromosomal" Sex.*—Rather to the chagrin of the geneticists, one of the important recent cytogenetic discoveries was made by an anatomist, who deserves great credit for perceiving a phenomenon that biologists must have been seeing for a long time. (It is some comfort to this geneticist that at least it was a Canadian anatomist!) Professor Barr and his associates,[14] while studying the neurological effects of fatigue, noticed that in female cats the majority of cells of the hypoglossal nuclei contained a special mass of nuclear chromatin, probably formed by fusion of heteropyknotic regions of the two X chromosomes. In males, who have only one X chromosome, most nuclei do not show a chromosomal mass of comparable size, although according to Sachs[163] both X and Y chromocenters are identifiable. Thus it became possible, for the first time, to determine the chromosomal sex of an individual by microscopic examination of somatic tissues. Such differences were soon shown to exist also in human tissues, including skin, buccal, vaginal or urethral mucosa, interstitial testicular tissue, and leukocytes. They appear to be already present in 3-week-old embryos, well before there is any gonadal differentiation.[198]

This observation has led to many intriguing discoveries, particularly as regards errors of sex development.[8, 13, 37] Patients with the condition formerly known as "ovarian agenesis" or Turner's syndrome, for instance, have been shown to have male type nuclei in about 90 per cent of cases, and the condition is more properly named "gonadal dysgenesis." A number of cases of Klinefelter's syndrome, or "testicular" dysgenesis, have been shown to have female type nuclear chromatin.[150] The method can be useful in helping to distinguish cases of female pseudohermaphroditism (congenital adrenal hyperplasia) from externally similar cases of gonadal dysgenesis, and in diagnosing cases of male pseudohermaphroditism that may have completely female external genitalia. (It is recognized, however, that clinical and social considerations may be more important than the "chromosomal sex" in determining whether a child should be brought up as a girl or a boy.[12])

A number of other interesting applications of "chromosomal sexing" have been reported, including the diagnosis of fetal sex by examination of amniotic cells and the suggestion that this could be used to predict which unborn babies were likely to inherit sex-linked recessive diseases[164] (though amniotic puncture may involve some hazard to the young embryo[179]). Examination of placenta has shown that

most, if not all, of the tissue of placental septa is maternal in origin,[165] and examination of teratomas shows that those arising in females have female type chromatin, while those arising in males sometimes have the female type of sex chromatin and sometimes mixtures of both.[8] Sex chromatin has also been used as a "tag" for demonstrating that tissue from an area where a male baby's skin had been grafted to his mother was, in fact, donor skin.[145]

Professor Barr's original observation on cat brains has thus thrown much light on sexual development and other problems in humans, and many more interesting discoveries are expected in future years.

IV. POPULATION GENETICS

Population genetics deals with the factors that influence the frequencies of genes in a population. This includes both "natural" populations, and "domestic" populations, where increasing the frequency of favorable genes can be economically profitable. In the field of animal breeding, techniques of sperm storage and artificial insemination and more effective methods of selection provide better means of breed improvement.[111] Our knowledge and social maturity are still inadequate for the application of such means to improvement of the human species, although the depressing prospect exists that they might quite possibly be applied to humans if a sufficiently powerful totalitarian government decided to enter the field of eugenics. Of more immediate interest is the fact that inherited diseases are becoming increasingly important causes of ill-health, and for this reason the findings of population genetics are of great significance to all those interested in human welfare. How much, for instance, are we increasing the frequencies of deleterious genes by improving our treatment of diseases that have a genetic component and thus increasing the chance that affected persons will have children? And how much are the mutations caused by the constantly rising level of exposure to high-energy radiation contributing to public ill-health? Some authorities have claimed that if these trends continue, humankind will inevitably degenerate into a race of malformed, disease-ridden imbeciles. Others take a less pessimistic view,[147] and we do not yet know enough to resolve the conflict. There are, however, a number of recent trends that may indicate the direction of future progress.

A. *Maintenance of Deleterious Genes in Populations.*—It is now becoming evident that the forces influencing gene frequencies are more subtle in nature and more complicated in their interactions than was previously realized. It used to be very simple—natural selection reduced, and mutation increased, the frequency of deleterious genes, while migration and "drift" (the result of random variations in small populations) altered the frequency in either direction depending on the particular situation. The mutation rate could be calculated simply as the amount of mutation necessary to replace the genes lost by selection.

It now appears, however, that the situation is much more complicated than this.[41] Natural selection acts

not on genes, but on individuals, and in this respect the effects of natural selection on the frequency of a particular gene depend on what other genes are present, and on the environmental situation. Furthermore, there appear to be factors other than mutation that can increase the frequencies of deleterious recessive genes. Dunn[43] has shown that mutant forms of a gene causing vertebral malformations occur surprisingly often in wild mouse populations. This is apparently not because of a high mutation rate, but because the gametes of mice carrying the mutation are not produced in the usual 50:50 ratio; instead there is an excess of gametes carrying the mutant gene. It has been calculated[24] that only a small segregation advantage would keep a deleterious gene in a population without the need for replenishment by mutation at all. It will be interesting to see whether such a phenomenon can be demonstrated in humans.

Another mechanism for maintaining the frequency of a deleterious recessive gene in a population is the phenomenon of heterozygote advantage. It is now clear from animal experiments that some genes that are obviously harmful when present in a double dose (homozygous) are actually beneficial to the organism in a single dose (heterozygous). Only a limited number of examples of this phenomenon have been discovered so far, and most of the relevant information comes from the lower organisms, but there is at least one clear-cut example of heterozygote advantage in humans. There is a gene, h^A,* responsible for a step in the synthesis of normal hemoglobin. An abnormal form of the gene, h^S, is responsible for the formation of an abnormal hemoglobin, causing the red blood cells to sickle under reduced oxygen tension. Persons homozygous for the abnormal gene (h^Sh^S) develop a fatal hemolytic anemia. Persons heterozygous for the gene (h^Ah^S) have the sickle cell trait, but no overt disease. The interesting thing is that persons heterozygous for the gene are unusually resistant to malaria, so that in a region where malaria is endemic, the heterozygotes are at a selective advantage,[2] which is apparently why the gene is so common in certain parts of Africa and the descendants of emigrants therefrom. Thus a gene that kills the individual in the homozygous condition can actually be advantageous to the heterozygote! We have yet to discover how widespread and important this phenomenon may be in humans.

Other examples of factors influencing gene frequencies include the recently discovered association of blood groups with certain diseases; e.g., group O people have an elevated frequency of peptic ulcer, and group A people appear to be predisposed to gastric cancer and diabetes.[117] This effect is so marked that a group O person is about 37 per cent more likely to develop duodenal ulcer than a person of some other blood group, and a group A person has about a 20 per cent increased probability of developing gastric cancer.[117] The exact interpretation of the statistical association is not yet entirely clear, but there seems no doubt that it exists, and that it has

*The nomenclature of the hemoglobins is still in a state of flux.[3]

important clinical implications. Furthermore there is the possibility that suppressor genes may exist in humans as in Drosophila[65] that inhibit the effects of nonallelic deleterious mutants and hence reduce the pressure of natural selection on them. Finally, the possibility exists that carriers of deleterious genes may overcompensate for their defective children by having more children than they otherwise would have. Such an effect has been demonstrated by Glass[61] in Rh-negative mothers of erythroblastotic babies.

Two points may be made. (1) There are factors other than mutation that can maintain deleterious genes in a population, but we do not yet know how important these may be. It is possible that such things as heterozygote and segregation advantage are more frequent in humans than was previously thought. If so, mutations would be comparatively less important as causes of ill-health. (2) It is much more difficult than was previously thought to make predictions about the effects of selection on the frequency of a particular gene. Thus the proponents of eugenic programs are having to revise their ideas about the effectiveness of eugenic measures. Suppose, for instance, it is shown that the recessive gene causing fibrocystic disease of the pancreas when homozygous is beneficial to the heterozygous carrier. Would we be justified in advising the parents of an affected child not to have further children, on the grounds that they will be increasing the gene frequency? Much more information is needed before one can answer such difficult questions, and it can be considered a real advance that the need for caution in making eugenic predictions is now widely accepted among human geneticists.

B. *Genetic Hazards of Radiation.*—The advent of the atomic age, and the inevitable increase in exposure of human populations to high energy radiation, has created an important practical problem for population geneticists. When the genetic implications of the rising radiation background aroused public concern, and the geneticists were asked to predict just how much ill-health would be caused by a given amount of radiation, we were found to be woefully ignorant. One bit of good blown by the ill-wind of atomic warfare may be the fact that increased public interest in, and support of, research in medical genetics will, quite apart from the radiation aspects, lead to a better understanding of the causes of disease, and thus to higher standards of medical care.

This article will not attempt to review the voluminous literature on the genetic hazards of radiation in humans. A number of very competent review articles are available.[64, 80, 122] Suffice it to say here, first, that there seems to be no doubt that the genetic effects of radiation are usually harmful, particularly if one accepts radiation-induced leukemia and bone sarcoma as examples of somatic mutation. Most of the arguments arise only about the extent of the harm, not about whether it exists. A recent claim that radiating human ovaries did no genetic harm to the first and second generation offspring[100] must be heavily discounted, since the data are inadequate to support the conclusion.

Second, by far the greatest proportion of radiation now received by human beings comes from diagnostic and therapeutic radiography. One should not, for this reason, withhold radiological examination or treatment which may protect or promote the health of the patient. One can, however, cut down appreciably the amount of radiation received, by eliminating unnecessary sources of radiation such as shoe-fitting machines, and by taking stringent measures to reduce the amount of radiation received by the gonads in radiological procedures to an absolute minimum compatible with good medical care.

V. MEDICAL GENETICS

A. *Experimental Mammalian Genetics.*—The importance of the lower mammals as experimental material for the investigation of medical problems is widely recognized. In cancer research, the use of inbred mouse strains has been invaluable in clarifying the complicated interactions of genetic and environmental factors underlying neoplastic change,[81] and in providing large numbers of mice which can be expected to develop a specific type of cancer with a predictable frequency, for use in screening new drugs of potential therapeutic value. Studies on inbred mouse strains have also helped to unravel the complicated web of gene-environment interactions underlying such things as body size[26, 46] and disease resistance[68, 194] and will provide useful guides to the analysis of such problems in humans.

Perhaps not so well appreciated is the existence of a great variety of inherited diseases in the lower mammals that should provide a great deal of valuable information about their human counterparts. These include a macrocytic anemia in the mouse,[162] cataracts in rats[171] and mice,[57] epilepsy in rabbits,[133] a type of hemophilia in dogs,[70, 88] osteopetrosis in rabbits[144] and mice,[72] retinal degeneration in mice[15, 174] and dogs,[113] deafness,[39] diabetes mellitus,[20, 115] muscular dystrophy,[125] pituitary dwarfism,[73] spastic paralysis[45] and spherocytosis[132] in mice, and many others. Since animals with the disease in question can be bred in virtually unlimited quantities, they provide an opportunity for studying the etiology, natural course, and therapeutic possibilities of the disease under uniform experimental conditions unachievable clinically. A great many such mutants are as yet unexplored pathologically and biochemically; here is a pool of potential information whose exploitation will lead to some of tomorrow's "recent advances."

B. *Genetic Study of Human Disease.*—The enormous amount of morphological, biochemical, and physiological information available on humans makes man in some respects a very suitable organism for genetic studies,[139] and some of the notable advances in biochemical and population genetics have been based on human material. But because of man's long generation time, small average family size, and disinclination to breed according to the wishes of geneticists, it will be some time before the sensational advances in the genetics of lower organisms will be fully matched in the field of medical genetics. Furthermore, human genetics got off to a bad start and is only

now beginning to recover from its early setbacks. One such setback followed the premature and overenthusiastic application of Mendelian principles to the problem of "race improvement." The culmination of this movement in the unfortunate excesses of the German Nazi regime has given the science of eugenics a bad name which has not yet been entirely erased. However, the modern "eugenic hypothesis" is a model of caution and sobriety.[32, 141]

Another setback to human genetics resulted from the fact that after Mendel's laws were rediscovered, a great deal of effort was spent trying to prove that Mendelian inheritance occurred in humans. This may have been a necessary state of affairs at the time, but it unfortunately led to a tendency for investigators to report, in the literature, cases of disease where the familial distribution supported the Mendelian hypothesis, and ignore clinically similar cases with no affected relatives. This resulted in the literature becoming "loaded" with familial cases and gave quite a prejudiced impression to the unwary reader. The acceptance of genetic principles in medicine must have been greatly delayed by such claims that were often so far from reality that their falsity must have been quite obvious to the observant clinician.

1. *Special statistical methods:* Recently, however, the great advances in control of infectious and nutritional diseases have led to a rapid upsurge of interest in the genetic components of disease, and hardly a week goes by without a description of some new genetic syndrome or a refinement in our knowledge of the genetic pattern in some disease. This trend has been greatly accelerated by the development of statistical techniques to handle the special problems of genetic analysis in humans.[139]

It is now recognized that in order to obtain an unbiased evaluation of the nature of the hereditary component in the etiology of a certain disease, one has to collect a consecutive series of cases, without regard to whether or not there are affected relatives, and then compare the familial distribution in the relatives with that in a suitable control series. Biases due to selection of familial cases can best be avoided by including all cases of the disease in a defined population, though this is usually very difficult. Noteworthy examples of this approach include the studies of Fogh-Andersen[50] on harelip and cleft palate, Grunnet[75] on diabetes mellitus, Crowe and associates[36] on neurofibromatosis, and Stevenson and Cheeseman[170] on rheumatic fever. The data thus collected can be most useful in supplying estimates of risk rates for advising families with affected members about the probabilities of occurrence of the disease in relatives.[53, 55, 56]

It is also necessary, of course, in analyzing such data, to allow for the fact that the families being studied are almost always ascertained by the fact that they contain an affected individual, so that this individual should not be included in calculations of the frequency of affected relatives. Failure to correct for this sort of bias had led to misleading statements about the inheritance of a number of diseases, e.g., poliomyelitis.[158]

2. *Heredity versus environment:* Twins may contribute useful information on the question of whether heredity is important in the etiology of a

disease, but only in so far as the series of twins is collected without regard as to whether or not they are concordant for the disease, and in so far as zygosity is correctly determined.[123, 186, 189] Since these requirements (particularly the former) are difficult to achieve, twin studies have not yet contributed a great deal to our knowledge of heredity in disease. Kallmann's twin-family studies on tuberculosis,[98] schizophrenia,[95] manic depressive psychosis,[95] and homosexuality[96] have been valuable in emphasizing the importance of genetic factors in these conditions. Simonds,[169] however, has recently demonstrated how extensive and subtle the biases can be in the collection of twin series, and her study casts doubt on the precision of most estimates of heritability in twins.

The use of monozygotic twins as experimental material, to compare effects of different dietary regimes, medical treatment, teaching methods, reactions to psychological situations, and so forth, seems to have been largely unexploited so far, although Robertson and associates[160] have used the method in a nutritional study and Glass[62] has presented some preliminary studies of muscular-visual precision in monozygotic twins and suggested how an extension of this type of study could provide useful data on the heritability of such things as adaptability.

One result of our improved understanding of the genetic factors underlying disease has been the virtual disappearance of the "which is more important—heredity or environment?" question. Although generalizations in this field are notoriously unreliable, it may be helpful to think of genetically influenced diseases in two major categories. First, there are a large number of diseases showing simple Mendelian patterns of inheritance,[53] each one being rare (because of the strong selective forces acting against them), but all together constituting an appreciable portion of the sum total of human ills. Second, there are much commoner diseases such as diabetes mellitus, rheumatic fever, epilepsy, and many of the common malformations, that show familial distributions, but not according to simple Mendelian patterns. Here the situation often seems to be that one clinical category contains a number of etiologically different types, including a minority of cases with a more or less clear-cut Mendelian pattern of inheritance and a majority of cases due to various combinations of multiple genetic and environmental factors, their interactions determining whether a given individual crosses the nebulous border line between normality and disease.[56] Epilepsy is certainly a heterogeneous clinical category,[142] and similar situations have recently been suggested for diabetes mellitus[75] and schizophrenia.[140] In the case of harelip and cleft palate, about 1 per cent of the cases seem to be associated with labial cysts which show simple dominant inheritance,[181] and the rest show a familial distribution[50, 54] but no clear-cut pattern. Experimental studies on cleft palate would suggest that the defect can be produced in several ways, each involving a combination of several genetic and environmental factors.[58] In view of this situation, generalized statements about whether heredity or environment is more important in causing a disease appear futile, to say the least.

C. *Detection of Genetic Carriers.*—One of the most important developments in medical genetics from a practical point of view is the matter of detecting the carriers of genetic diseases, i.e., those persons who are able to transmit a gene for a given disease to the offspring, but who do not have the disease themselves, either because the gene is recessive and the person is heterozygous for it, or because for some reason or other a dominant gene has failed to express itself (reduced penetrance). In both cases, detection of heterozygous carriers would be useful to the counselor, who wishes to know which relatives of an affected person may transmit the gene to their children. The sisters of hemophiliac males, for instance, have a 50:50 chance of inheriting the hemophilia gene from their mother (in which case they are likely to have affected sons) or inheriting the normal gene from their mother and having only unaffected sons. It would be a great advantage in advising such families to know which females had in fact inherited the hemophilia gene. Similarly, an albino who was contemplating marriage might value the possibility of detecting, by transillumination of the iris, that his prospective mate was a carrier of the albino gene.[47]

In the case of reduced penetrance, it would be valuable to identify carriers not only in order to predict which individuals might have affected children, but to study the circumstances associated with failure of the gene to manifest itself, with the hope of finding ways in which the gene effects could be suppressed therapeutically.

Neel,[134] in 1947, drew attention to the importance of carrier detection in genetic counseling and other aspects of medicine, and Hsia[84] has recently reviewed progress in the laboratory detection of the heterozygous carriers of hereditary diseases. Noteworthy advances have been made, and Hsia lists the following recessive conditions in which there is reliable evidence that heterozygotes can be detected: adrenal hyperplasia, afibrinogenemia, cystinuria (one type—see section V, E, 1), congenital hypothyroidism with goiter, fibrocystic disease of the pancreas, galactosemia, hypophosphatasia, idiopathic hemochromatosis, labile factor deficiency, nephrogenic diabetes insipidus, phenylketonuria, PTC deficiency, sickle cell anemia, SPCA deficiency, and thalassemia. Suggestive, but not conclusive evidence has been presented for diabetes mellitus, Gaucher's disease, glycogen storage disease, hemophilia (mild type), hypoglycemosis, idiopathic hypoprothrombinemia, idiopathic hyperlipemia, juvenile amaurotic idiocy, Neimann-Pick's disease, PTA deficiency, and Wilson's disease. Further advances in this field are confidently to be expected, with consequent benefit to patients and their relatives.

D. *Genetic Counseling.*—Advances in the field of genetic counseling stem from the increase in, and refinement of knowledge about, the genetics of the diseases about which counseling problems arise,[146, 185] and the growing realization that counseling families about genetic problems is not just a matter of making a statistical prediction, but requires evaluation of the whole family situation including psychological, social, religious, economic, and domestic factors. Proper interpretation of the statistical prediction

within these terms of reference may often require consultation with a priest, psychiatrist, family physician or marriage counselor.[55, 97] The demand for genetic counseling is growing and there is an increasing need for suitably trained counselors as it becomes recognized that the procedure can be helpful.

E. *Applications of Genetic Principles to Medical Problems.*—To demonstrate how genetic methods can be useful in helping to solve medical problems, the author has chosen, from a number of possible cases, two specific examples.

1. *The genetics of cystinuria:* The studies of Harris and others[77, 78] have helped greatly to clarify the confusion about the inheritance of this disease. They found that the families studied fell into two groups. In one group cystinuria shows simple recessive inheritance. The homozygotes for the recessive gene excrete abnormally large amounts of cystine, lysine, arginine, and ornithine, and frequently form stones, whereas the heterozygotes have normal urinary amino acid excretion. In the other group the homozygotes are indistinguishable from those of the first group, but the heterozygotes show a moderately increased excretion of cystine and lysine, and form stones occasionally. Thus the clinical disease, cystinuria, can be due to homozygosity for one of at least two different gene pairs. (A situation where several different genes can each produce the same clinical entity is well known in the lower organisms and seems to occur quite often in humans, e.g., deaf-mutism,[177] fibrocystic disease of the pancreas,[20] glycogen storage disease,[31] hemophilia,[69] and perhaps thalassemia.[138])

Harris' study also represents an ingenious application of family studies to the elucidation of a physiological problem. He studied urinary excretions of cystine, arginine, and lysine in cystinuric patients and their relatives. Because the heterozygotes for one of the cystinuria genes show intermediate levels for cystine excretion he was able to correlate the excretion of cystine in members of cystinuric families with that of the other two amino acids over a wide range of excretory levels. A positive correlation was found between cystine and lysine over the whole range from 20 to 800 mg. cystine per gram of creatinine. On the other hand, the excretion of arginine does not begin to rise until the cystine level approaches 250 mg. per gram of creatinine and then rises rapidly. This leads to the suggestion that a normal renal tubular resorptive mechanism which is at one stage specific for cystine, lysine, arginine, and ornithine is defective in cystinuric patients. When it is completely defective, all four amino acids are excreted in excessive amounts, but when it is only partially defective, arginine and possibly ornithine are resorbed preferentially to cystine and lysine. If one postulates a carrier substance that transfers these four amino acids across the tubular wall, it follows that arginine has a greater affinity for the carrier substance than has cystine or lysine.[78] Thus the genetic approach has provided precise information for the use of genetic counselors in predicting which family members will be susceptible to stone formation and has also contributed to the understanding of normal kidney tubular function.

2. *The hemoglobins:* Probably the most outstanding recent advance in medical genetics is the analysis of gene-determined differences in hemoglobin structures and particularly that associated with sickle cell disease. The familial nature of sickle cell anemia was recognized shortly after the disease was first described, but no distinction was made between the sickle cell trait (sickling of the red cells under reduced oxygen tension) and sickle cell anemia—both were thought to be due to a dominant gene with variable expressivity. Great credit goes to Neel,[135, 136] who systematically examined the relatives of a series of patients with sickle cell disease and showed that: (1) in almost every case of sickle cell disease both parents were found to have the sickle cell trait,[135] (2) in the offspring of parents with the sickle cell trait a ratio of 1 normal:2 sickle cell trait:1 sickle cell disease was found[136]; and (3) the children of patients with sickle cell disease married to nonsickling spouses all had the sickle cell trait.[137] These facts lead irresistibly to the conclusion that the sickle cell trait is produced by the sickle cell gene in combination with the normal form of the gene, and that sickle cell disease is caused by the sickle cell gene in double dose. The rare exceptions to point (1) above could be accounted for on the basis of illegitimacy, or interaction of the sickle cell gene with a gene for another abnormal hemoglobin (see below).

Shortly after Neel's original report, Pauling[143] showed that the blood of patients with sickle cell anemia contained a "defective" hemoglobin separable from normal hemoglobin by electrophoresis. Blood from persons with the sickle cell trait contained both normal and sickle cell hemoglobin in the same erythrocytes, as if each gene were determining the structure of its own hemoglobin molecules, independently of the other member of the gene pair. The idea (stemming largely from the work on Neurospora[157]) that genes act by imprinting their specificities on enzymes or other protein molecules was thus brought into the medical limelight, and this led to the concept of "molecular diseases." This line of thinking has undoubtedly been one of the factors responsible for the above-mentioned upsurge of interest in the biochemical detection of carriers of disease, and for the discovery of a specific enzymatic defect in a number of genetically determined diseases such as galactosemia,[94] the various forms of glycogen storage disease,[31] hypophosphatasia,[52] and phenylketonuria.[128]

To return to the genetics of sickle cell disease, another important development has been the recent demonstration by Ingram[90, 91] that sickle cell hemoglobin differs from normal hemoglobin in only one of about three hundred amino acids that constitute the polypeptides of the hemoglobin molecule—a particular glutamic acid in one of the peptides of the normal hemoglobin molecule is replaced by a valine molecule in sickle cell hemoglobin. Thus a single gene substitution has been identified, for the first time, with a subtle but specific change in the structure of a protein molecule—no closer approach to understanding the mode of action of a gene has yet been made.

Not long after the genetics of sickle cell disease was elucidated, another

abnormal hemoglobin, hemoglobin C, was identified, also by its characteristic electrophoretic mobility.[92] Heterozygotes for this gene are usually asymptomatic, but the homozygotes have a mild hemolytic anemia, with splenomegaly.[170] This gene appears to be a mutation at the same locus as the sickle cell gene, and a person inheriting both mutant genes has a severe hemolytic anemia similar to that of a person with sickle cell anemia.[129]

A number of other abnormal hemoglobins are now recognized, and no doubt their nomenclature will soon outstrip the alphabet. Hemoglobin G appears to be a normal variant, and to involve a different genetic locus from S and C. Hemoglobins D, E, I, and J are not yet sufficiently well studied to determine their relationships to the other mutant types. Hemoglobin H is unusual in that it appears only in persons who are also heterozygous for the gene for thalassemia.[131] Hemoglobin M, recently identified by starch electrophoresis, is associated with congenital methemoglobinemia.[59] The gene for thalassemia, which in the heterozygote produces thalassemia minor, and in the homozygote produces the much more serious and fatal thalassemia major, seems to be inherited independently of the loci for S and C and for G hemoglobins.[167] However, persons heterozygous for the T gene and heterozygous for either the hemoglobin S, C, or E gene manifest a severe anemia. It appears that family studies in cases of hemolytic anemia, including electrophoretic analysis, may provide the pediatrician with highly useful information, both from the point of view of diagnosis and for counseling the parents of such cases about the possibility that severe hemolytic disease may occur in future siblings or other relatives of the patient.

The puzzle presented by the high frequency of certain abnormal hemoglobins in certain areas of the world and the partial answer provided by the fact that heterozygous carriers of the sickle cell gene are relatively resistant to malaria have been discussed earlier in this paper and are well reviewed by Neel.[138] Besides the previously mentioned eugenic implications of this discovery, there are significant anthropological and evolutionary considerations that cannot be reviewed here. The discovery, by the application of simple genetic principles, of the mode of inheritance of sickle cell anemia has led to findings of such fundamental importance, and with such widespread ramifications, that it represents an outstanding landmark in the history of medical genetics.

3. *Other developments:* Space does not permit the discussion of many other important developments in medical genetics, such as the use of tissue culture in studying the biochemistry of genetically determined diseases,[22] the use of dermatoglyphics in the diagnosis of Mongolism,[188] the discovery of genetically determined variants in the serum proteins,[172] the existence of blood group chimeras, possibly due to fusion of placental circulations in dizygotic twins in some cases,[44] but not in others,[33] the use of hereditary agammaglobulinemia to study the origin, fate, and function of gamma globulin,[60] and many others. There will be no lack of material for future review articles on recent advances in medical genetics.

In a previous article[53] the writer provided a list of diseases of pediatric interest and what was known about their familial distributions. The following items represent some additions to and modifications of the previous list.

Agammaglobulinemia. The "congenital" form usually shows sex-linked recessive inheritance.[60]

Agranulocytosis, infantile. Recessive.[107]

Anemia-hemoglobin C disease. See text.

Anemia, hemolytic, nonspherocytic. May present as hemolytic disease of the newborn. Dominant.[35]

Anencephaly. 0.75-3.7/1,000 births.[148] *Average* risk for siblings about 5 per cent of having anencephaly or spina bifida aperta.[56, 148] Higher in some families?

Arthrogryposis multiplex congenita. May occur in siblings. Genetics not clear.[28]

Cleft lip with labial cysts. Dominant with somewhat reduced penetrance. About one-half the cases have a cleft lip and palate as well. These represent about 1 per cent of cleft lips.[181]

Convulsive disorder. May be a symptom of specific inherited disease such as amaurotic idiocy, epiloia, phenylketonuria, or sickle cell anemia. For "centrencephalic" ("idiopathic," "essential") epilepsy, risk for sibs being "chronic" epileptics is about 5 per cent.[56, 124]

Cretinism, goitrous, nonendemic, often occurs in siblings.[195] Possibly recessive. The athyreotic type occasionally occurs in siblings.[30]

Dentinogenesis imperfecta. May occur as part of osteogenesis imperfecta, or as a separate entity with dominant inheritance.[87]

Diabetes mellitus. 1/100. Probably etiologically heterogeneous. Occasional dominant pedigrees with somewhat reduced penetrance.[25] Some studies suggest recessive inheritance with reduced penetrance.[76, 149, 175] Siblings of severe cases (fasting blood sugar over 200 mg. per cent, ketonuria, requiring insulin), with normal parents, have an empirical risk of 5 per cent of developing diabetes before age 20, 11 per cent before age 60.[75] Offspring of a diabetic (other parent normal) has about a 5 to 15 per cent chance of developing diabetes before age 30.[40, 56]

Dwarfism, with brachydactyly and spherophakia (Marchesani's syndrome). Recessive, with mild manifestations in the heterozygote.[104]

Elliptocytosis. Dominant. Linked to ABO blood group locus.[109]

Endocardial fibroelastosis. Primary type recurs in siblings, possibly recessive inheritance.[101]

Factor V deficiency. See parahemophilia.

Factor VII deficiency. See SPCA deficiency.

Galactosemia. Probably recessive; heterozygotes sometimes have abnormal galactose tolerance.[83]

Glycogen storage disease. At least four different types, each probably recessive, each with a block at a different step in the metabolism of glycogen.[31]

Glycosuria, renal. Often dominant.[103]

Hartnup disease. Pellagra-like rash, with ataxic episodes and renal amino-aciduria. Probably recessive.[11]

Heart disease, congenital. Etiologically heterogeneous. Risks for heart malformations associated with syndromes such as mongolism, Marfan's syndrome, chondrodystrophia calcificans congenita, the Ellis-van Creveld syndrome, and the maternal rubella syndrome will depend on recurrence risk for the specific disease. Excluding these, *average* risk for siblings (parents normal) is 2 per cent or less for coarctation of the aorta, interauricular septal defect, interventricular septal defect, patent ductus arteriosus, isolated pulmonary valvular stenosis, and tetralogy of Fallot.[6, 56, 108, 119, 151]

Hyperostosis cortical, infantile (Caffey's disease). May occur in siblings.[168] Genetics not clear.

Hypoglycemosis, idiopathic, infantile. Often occurs in siblings.[7]

Hypophosphatasia. Probably recessive, with some heterozygotes having low serum alkaline phosphatase and/or phosphorylethanolaminuria.[52]

Hypospadias. Risk for brothers 9 per cent.[173]

Leukocytes, unsegmented. See Pelger-Huet anomaly.

Leukemia. Risk for siblings very low,[182] except in a few families.[45]

Lobster-claw malformation. See split hand deformity.

Marchesani's syndrome. See dwarfism with brachydactyly and spherophakia.

Mongolism. Risk for siblings of an affected child about 1/800 when mother is age 25, rising to about 1/16 if mother is 45.[146]

Nephrosis, idiopathic. May occur in siblings, but rarely.[49]

Parahemophilia (Factor V, labile factor, accelerator-globulin deficiency). Probably recessive, but heterozygotes have asymptomatic mild factor V deficiency.[84]

Pelizaeus-Merzbacher disease. Sex-linked recessive; or autosomal dominant in males, recessive in females.[153]

Pellagra-like rash with ataxia and amino-aciduria. See Hartnup disease.

Pentosuria. 1/50,000. Urinary excretion of l-xyloketose (recessive) or dl-arabinose (dominant).[103]

Posterior-root degeneration. See sensory radicular neuropathy.

Progeria. May occur in siblings; genetics not clear.[130]

Pseudohemophilia (Von Willebrand's disease). Usually dominant, but occasional family sex-linked recessive.[114]

PTA deficiency (plasma thromboplastin antecedent deficiency). Dominant with variable expression.[161]

Puberty, precocious, constitutional. Dominant, not expressed in heterozygous females.[93]

Pyelonephritis, interstitial, with nerve deafness. Dominant; fatal in males, mild or asymptomatic in females; may be partially sex-linked. Affected males may have cataracts. Disease may resemble acute glomerulonephritis or nephrosis at some stages.[67]

Pyloric stenosis, hypertrophic. 3/1000, 5♂ : 1♀. Risk for siblings, 6 per cent.[118] For offspring 7 per cent.[120] For siblings of affected child with affected parent, 40 per cent.[120]

Radial absence. Dominant in some families.[42] Often sporadic. Sometimes occurs with Fanconi's aplastic anemia (probably recessive).[105]

Renal anomalies with malformed ears. Attention has been drawn to the association between malformed ears and malformed kidneys and/or ureters.[82] Though it is not yet clear how many cases of malformed ears have kidney anomalies, the association may be diagnostically useful.

Renal aplasia, with peculiar facies ("Potter's syndrome"). May occur in siblings, but rarely.[10]

Retinoblastoma. Dominant with about 80 per cent penetrance.[48, 183] "Sporadic" cases may be germinal mutations (risk for children 40 per cent) or somatic mutations or phenocopies (risk for children 0). Sixty per cent of cases are bilateral, which are more likely to be mutations than unilateral ones. Average risk for siblings of a sporadic case about 1 per cent. Average risk for offspring of a bilateral case about 20 to 40 per cent, for offspring of a unilateral case about 5 to 10 per cent.[183]

Rheumatic fever. Genetic predisposition to rheumatic reaction to streptococcal infection said to be recessively inherited,[196] but others disagree.[176, 180] Estimates of average risk for siblings (parents normal) in temperate climates and lower income groups range from about 8 per cent[176, 180] to 22 per cent[196]; for siblings, with one parent affected, about 20 per cent[176, 180] to 45 per cent.[196]

Rubella syndrome (cataract, congenital heart disease, deafness). On the relatively small amount of data now available, if maternal disease occurs in first trimester, risk for child is roughly 15 per cent of being malformed, 5 per cent of being stillborn. Similar values apply in the second trimester, particularly in the fourth month.[89]

Sensory radicular neuropathy. Dominant.[79]

SPCA deficiency (Serum Prothrombin Conversion Accelerator, factor VII, proconvertin, stable factor deficiency). Perhaps recessive, with heterozygotes showing slight prolongation of prothrombin time.[157]

Split hand (and foot) deformity. 1/90,000. About 1 in 5 have affected relatives—in these families pattern is dominant with somewhat reduced penetrance. Risk for

siblings of a "sporadic" case about 6 per cent. Bilateral "sporadic" cases likely to be mutations, unilateral ones almost always nonfamilial.[19]

Thrombocytopenic purpura. Usually not familial. Rarely dominant.[137] A rare type *with dysentery and eczema* is sex-linked recessive.[1]

Von Willebrand's disease. See pseudohemophilia.

Waardenburg's syndrome. Deafness, with lateral displacement of medial canthi, broad high nose, heterochromia iridum, white forelock. Dominant, with 50 per cent penetrance.[184]

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Comments on Current Literature

CHELATING AGENTS IN THE TREATMENT OF HEPATOLENTICULAR DEGENERATION (WILSON'S DISEASE)

IT IS now generally accepted that Wilson's disease[1] (hepatolenticular degeneration) is characterized basically by an inherent inability to synthesize the copper-binding serum protein, ceruloplasmin, with resultant accumulation of copper in the body, especially in the liver and in the brain.[2-4] Urinary excretion of copper is increased, and the level of copper in the plasma decreased, in this condition. Ceruloplasmin is described as an alpha globulin having oxidase activity, whose blue color is due to a copper content of eight atoms per molecule. Normally this protein fraction comprises about 0.5 per cent of the total serum proteins, being of the order of 30 mg. of ceruloplasmin per 100 ml. of serum. In Wilson's disease there may be a marked reduction in the concentration of this copper-binding serum protein. As much as 60 to 80 per cent of the serum copper is unbound (i.e., to ceruloplasmin), as compared with the situation obtaining in normal persons in whom only about 10 per cent of the copper is not protein-bound.[3, 4] This deficiency in ceruloplasmin seems to be congenital and has a definite familial tendency. In time, the copper content increases in the cirrhotic liver and in the degenerating lenticular nucleus of the brain. Characteristically the degenerative process involves the basal ganglia.

In most instances the disease becomes manifest clinically in the latter part of childhood, and is characterized by a rigidity of the skeletal musculature and by involuntary movements; there may be marked emotional lability and convulsive laughter without apparent provocation. The facial appearance is usually one of constant smiling; the speech becomes jerky and irregular. While the involuntary movements may be of any type, tremors involving the upper extremities more than the lower are characteristic. Usually the tremor is present at rest, as in paralysis agitans, but it is most marked in association with voluntary movements. In older children, as a rule, the hepatic symptoms are not obvious; liver function tests are not of particular diagnostic value; however, the cephalin flocculation test is often positive. In infants and young children, on the other hand, the presenting symptoms may be those of hepatic disease, and, in this age group, the diagnosis of hepatolenticular degeneration is a possibility in unexplained cirrhosis. In the adolescent patient, tremor is commonly the initial sign, and is often diagnostic in type, particularly if at rest it resembles the parkinsonian tremor, to become on purposive movement a marked ataxia with choreiform components. This characteristic gross tremor involving the upper extremities has been described as *Fluegelschalgen* (flapping). While the duration of the disease varies widely, the course is invariably progressive, with associated mental changes. That the condition has a high familial incidence was noted by Wilson,[1] himself, an observation borne out by those of other clinicians through the years. Frequently more than one sibling in a family is affected. In about one-third of the cases investigated by Bearn[5] in 1953, the parents were

known to be cousins. The high incidence of the condition among siblings, both boys and girls, children of parents free of the disease, together with known consanguinity in some affected families, has made an autosomal-recessive genetic pattern seem likely.

While hepatolenticular degeneration is primarily a metabolic disorder, and was recognized as such early, the dramatic nature of the nervous system manifestations had placed the condition largely in the province of the neurologist. Within recent years, however, a new approach to Wilson's disease has been made possible by the rapidly developing biochemical methods in clinical medicine, and during the last decade fundamental advances have been made with respect to its pathogenesis and treatment. In 1952 Scheinberg and Gitlin[3] reported that ceruloplasmin, the blue copper-binding alpha-globulin first described by Holmberg and Laurell[6] five years previously, was deficient or absent in patients with hepatolenticular degeneration. This important observation has been extended and elaborated to cover many of the facts concerning Wilson's disease, and recent studies on copper metabolism, especially those with radioactive copper, have opened the way to a better understanding of the condition. These advances are summarized in an excellent review article by Walshe,[4] appearing in the *British Medical Bulletin* for May, 1957, who states that the primary biochemical defect is a failure to synthesize ceruloplasmin which in Wilson's disease may be greatly reduced or absent entirely. "Associated with this, though not necessarily secondary to it, is an excess absorption of copper from the gut. Owing to the deficiency of ceruloplasmin, copper is not tightly protein-bound and remains as free or direct reacting copper, loosely complexed to albumin. This allows it to be deposited in the tissues, where it accumulates. The organs principally affected are the liver, leading to cirrhosis; the brain, leading to cellular death and gliosis; and in the kidney, leading to aminoaciduria and glycosuria."[4] Walshe states that in time the copper accumulating in these organs is chelated by amino acids and peptides and overflows into the plasma, where it is present as direct reacting copper, and eventually is excreted in increased amounts in the urine.

Walshe refers to radioactive copper studies (Cu^{64}) by several groups of investigators, many of which support the foregoing hypothesis. Radioactive copper when taken by normal subjects either orally or intravenously, rapidly reaches a peak concentration in the blood attached to serum albumin. It then disappears, to return in about 12 hours bound to the ceruloplasmin fraction. In patients with Wilson's disease, this biphasic curve is not observed; instead, the copper, after reaching a peak concentration, falls off very slowly. "As compared with normal subjects, much of this copper is excreted in the urine, very little in the stools, and a high percentage of the total dose is retained in the body. It has been estimated that, when on a normal diet, patients with Wilson's disease may be in positive copper balance by as much as 2 mg. daily."[4] On the premise that the symptoms of Wilson's disease stem from this accumulation of copper in the body, therapy has been directed toward removal of the copper excess in order to arrest the progress of the disease before irreversible damage occurs in the cerebral cortex and the basal ganglia. Following the discovery that British Anti-Lewisite (BAL) is capable of mobilizing copper from normal subjects, this substance (2,3-dimercaptopropanol) was used effectively in the treatment of Wilson's disease.[2] However, repeated intramuscular doses are necessary, some cases are resistant to the treatment, and in some patients toxic manifestations have been severe. Other means shown to be effective in increasing the urinary excretion of copper have included the use of intravenous Versene, intravenous amino acids, cortisone, and increased dietary protein intake.[7]

While BAL has been used with considerable success in combination with a high protein diet and potassium sulfide or a form of Carbo-Resin after meals, in order to reduce the absorption of copper from the gut, the severe toxic manifestations and growing resistance have limited its usefulness.

It was shown recently that the sulfhydryl amino acid, penicillamine (dimethyl cysteine), is of value in removing copper from patients with hepatolenticular degeneration. Walshe[4] described its use, its rationale, and compared its effectiveness with that of BAL in two reports in 1956. Penicillamine hydrochloride "in doses of 0.5 to 1.5 g. by mouth daily, produced a tenfold increase in the excretion of copper in two normal subjects, as well as in six patients with Wilson's disease."[4] In five of these patients the copper excretion following penicillamine was greater than that obtained by the administration of BAL. Following the lead of Walshe, Bearn[7] treated two patients with penicillamine, reporting the results in May, 1957. Penicillamine was identified first as a breakdown product occurring in the urine of patients with liver injury who were receiving parenteral penicillin. The substance proved to be a sulfhydryl amino acid, β, β-dimethyl cysteine. When isolated from urine it is in the reduced state, giving a characteristic blue color reaction with ferric chloride which is not given by the disulfide-tetramethyl cystine. Penicillamine is stable in the reduced form, is extremely soluble, and is excreted rapidly by the kidney. The compound can be synthesized from penicillin, and occurs in L, D, and racemic forms. Penicillamine hydrochloride has been given orally in gelatin capsules in doses up to 1.5 Gm. daily, the maximum single dose being 500 mg. before meals, and with no addition of alkali to neutralize the hydrochloric acid. When administered intravenously, a molar amount of bicarbonate is added immediately before administration. Seitz filtration insures sterility, and no apparent toxic side effects have been observed following either the oral or the intravenous preparation.

In January of this year, two clinical reports appeared dealing with the use of penicillamine hydrochloride in Wilson's disease, one by Osborn and Walshe[8] in *Lancet*, and one in the Canadian literature by Fister and his associates.[9] Osborn and Walshe studied the comparative efficacy of intramuscular dimercaprol (BAL) and oral penicillamine in one normal subject and three patients with Wilson's disease, approaching the problem from the standpoint of Cu^{64} turnover. The results showed "clearly that penicillamine is very active in promoting the excretion of copper and appears to be superior to dimercaprol in this respect."[8] On the basis of this pilot study, the authors conclude that "in healthy people almost all the injected copper becomes firmly bound to protein by twenty-four hours, whereas in patients with Wilson's disease it mixes with a large body pool of copper and remains readily available for excretion at the glomerulus."[8] The report by Fister and his associates[9] concerns a family of four children, two girls apparently unaffected, and two boys, both of whom developed Wilson's disease. The clinically apparent onset in both boys occurred at 13 years of age; however, in the case of both of these patients, there had been a severe gastric upset with diarrhea, vomiting, and jaundice at the age of 10. In the elder, manifestations of hepatolenticular degeneration were severe on admission to the hospital; the course was progressively downhill, and in spite of energetic therapeutic measures, the boy died from intractable hemorrhage of the esophagus. In the case of the second boy in this family, medical advice was sought early in the disease. At the time of the published report this patient had been under treatment for four years. Early treatment included the usual supportive measures together with the administration of BAL, then of calcium versenate, the

therapeutic regimen being carried out at home after his discharge from the hospital. This treatment did not prove satisfactory, and the patient experienced repeated relapse with increasing severity of symptoms. Treatment with penicillamine was begun Dec. 1, 1956, following the regimen outlined by Walshe. Improvement was dramatic; the urinary excretion of copper was markedly increased; the downhill course of the patient was arrested, with improvement steady and consistent. The authors attribute the better results with penicillamine to its abilty to bring about "a greater diuresis of copper than either, or both, of the other agents." The steady improvement in this patient, who is now able to speak, write, and attend school for part of the day, has paralleled the degree of negative copper balance. A second case, the child of another family, is presently under initial treatment with penicillamine; the response to date is considered good. In the light of their experience, Fister and his colleagues[9] regard penicillamine as "a superior therapeutic agent for the treatment of hepatolenticular degeneration than previously available chelating agents," the compound having the "additional advantage of being effective orally." The optical isomers of penicillamine are identical apparently in their ability to bring about copper excretion in Wilson's disease.

While, as Walshe[4] has emphasized, the usefulness of penicillamine cannot be assessed fully except by long-term clinical trial, the reported "results are very encouraging and may well indicate that penicillamine will be a valuable advance in the treatment of Wilson's disease." Walshe likewise emphasizes that some aspects of the pathogenesis of this condition have not been explained as yet on the basis of ceruloplasmin deficiency alone, particularly the excess copper absorption from the gut. He[4] states, however, that if this explanation of the pathogenesis is accepted on the present evidence, it "places Wilson's disease alongside haemophilia and agammaglobulinaemia as a disease characterized by failure of synthesis of a single serum protein."

RUSSELL J. BLATTNER.

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News and Notes

The following were certified by the **American Board of Pediatrics** at the examination at Memphis, Tennessee, on March 21, 22, and 23, 1958.

Dr. John Andrea, 4820 Vernon Ave., N.W., Canton, Ohio.

Dr. William Henry Arnone, 232 Main Street, Brockton, Mass.

Dr. Carl P. Bernet, Jr., 401 Park, Greenwood, Miss.

Dr. Mauldin J. Boggs, North Main Street, Abbeville, S. C.

Dr. Quellin Thenard Box, 2051 Bay Street, Texas City, Tex.

Dr. Velta F. Briuks, Medical Arts Building, Oak Ridge, Tenn.

Dr. Clement E. Brooke, University of Missouri School of Medicine, Columbia, Mo.

Dr. C. Walter Brown, 1900 Brown Street, Alton, Ill.

Dr. Thomas Whittaker Browne, 1430 Ashby Avenue, Berkeley 2, Calif.

Dr. H. Gunther Bucheleres, 1753 W. Congress Parkway, Chicago 12, Ill.

Dr. Lyle Wendell Burroughs, 4215 Swann Avenue, Tampa 9, Fla.

Dr. Robert M. Butler, 3426 N. Meridian Street, Indianapolis, Ind.

Dr. Robert Edward Chambers, Akers Center, Gastonia, N. C.

Dr. Chris Nicholas Christu, 1417 5th Avenue South, Moorhead, Minn.

Dr. Richard Case DeGolia, 3019 Bellflower Boulevard, Long Beach 8, Calif.

Dr. Joseph Charles Denniston, Main Street, Lewisburg, Ky.

Dr. Melvin Ehrich, 266 Yazoo Street, Clarksdale, Miss.

Dr. Eugene U. Epstein, 3408 Hindman Ferry Road, Memphis, Tenn.

Dr. Robert McCreery Flowers, 1233 Forest Avenue, Columbus, Ga.

Dr. Bryant L. Galusha, 1419 Ferncliff Road, Charlotte 9, N. C.

Dr. Ruth Brinker Hamady, 228 Welch Blvd., Flint, Mich.

Dr. Charles Andrew Hanson, 17 South 4th Street, Geneva, Ill.

Dr. Forest Delbert Harris, 605 Gore Blvd., Lawton, Okla.

Dr. Samuel Allen Hartman II, 630 Chestnut Street, Lebanon, Pa.

Dr. Judson L. Hawk, Jr., 27 8th Street, N.E., Atlanta 9, Ga.

Dr. James Gilson Hawkins, 134 Hilands Place, Pittsburgh 9, Pa.

Dr. Gordon Read Heath, 1703 Sims Place, Lakeland, Fla.

Dr. Patricia Hornbeak Henderson, 6318 N. Van Ness Blvd., Fresno, Calif.

Dr. Edward L. Hendricks, 820 N.W. Skyline Crest, Portland, Ore.

Dr. Frederic C. Henry, 3745 Tall Oaks Road, Toledo, Ohio.

Dr. Leon Horowitz, 5538 East 26th Place, Tulsa, Okla.

Dr. Carolyn Coker Huntley, Baptist Hospital, Winston-Salem, N. C.

Dr. Robert F. Huxtable, 1501 S. Catalina Ave., Redondo Beach, Calif.

Dr. Howard H. Johnson, Jr., 421 Fenwick Drive, Falls Church, Va.

Dr. Barbara Jones, 500 S. Kingshighway, St. Louis 10, Mo.

Dr. John Kanas, 1428 Alamo, Colorado Springs, Colo.

Dr. Louis L. Keppler, Jr., 5500 Ridge Road, Parma, Ohio.

Dr. Maurice J. Lonsway, 9001 Green Ridge, Clayton 17, Mo.

Dr. Berton J. Mathias, 1301 Flushing Road, Flint, Mich.

Dr. William C. McCormack, 313 Fifth Street, Ames, Iowa.

Dr. Cecil Ray McEwen, Jr., 618 Main Street, Columbus, Miss.

Dr. Eric B. Meador, Jr., 2820 Lancaster Lane, Oklahoma City, Okla.

Dr. William D. Misbach, 4647 Burnet, Sherman Oaks, Calif.

Dr. Andrew Noble, 5450 Bond Street, Oakland, Calif.

Dr. Thomas Campbell Nolan, 803 Adams Avenue, Montgomery, Ala.
Dr. Donald E. Payne, 305 West Rusk, Tyler, Tex.
Dr. Robert Phillips Richardson, 19467 Monte Vista, Detroit 21, Mich.
Dr. Donald Glenn Ritter, Lincoln Clinic, Lincoln, Neb.
Dr. Keith I. Robins, 2710 Valley View Lane, Dallas 34, Tex.
Dr. Clifton Page Rose, 7826 Irwingrove Drive, Downey, Calif.
Dr. Bernard M. Roth, 5240 Woods Street, La Mesa, Calif.
Dr. Herbert Leon Ruben, 428 Marrett Road, Lexington, Mass.
Dr. Emilia Sedlis, 527 West 110th Street, New York 25, N. Y.
Dr. Nomie Abraham Shore, 1414 21st Street, Santa Monica, Calif.
Dr. Harris Lake Smith, U. of Tennessee, 860 Madison, Memphis 3, Tenn.
Dr. Meryleen Bailey Smith, West Virginia Hotel, Bluefield, W. Va.
Dr. Earle Spaugh, 1526 Harding Place, Charlotte 3, N. C.
Dr. Eleanor Stafford, 2507 McCallie Ave., Chattanooga, Tenn.
Dr. Willis Franklin Stanage, 400 Park Ave., Yankton, S. D.
Dr. Marjorie R. Stewart, 581 Golferest Dr., Dearborn, Mich.
Dr. James Walter Stone, 1131 Chestnut Hill Dr., Lynchburg, Va.
Dr. William Charles Taylor, 2500 Genesee St., Utica, N. Y.
Dr. Charles Arthur Tompkins, 841 E. 63rd St., Chicago 37, Ill.
Dr. Nils J. Tunestam, 2760 W. Foster Ave., Chicago 25, Ill.
Dr. Minnie Ratliff Vance, 2507 McCallie Ave., Chattanooga, Tenn.
Dr. Gerald G. Woodruff, Jr., 1301 Woodstock Ave., Anniston, Ala.
Dr. LeGrand Gardner Woolley, 460 Pierce St., Monterey, Calif.
Dr. John Moore Yeager, 1103 Eighth St., Alexandria, La.
Dr. Gilbert F. Young, Medical College of South Carolina, Charleston, S. C.

Special Foreign Certificates

Dr. Digumarthi Gopalaswami, 1614 Highland St., Apt. 2, Columbus 10, Ohio.
Dr. Sami El-Sheikh Kassim, 130/1 Karradat Mariam, Baghdad, Iraq.

Dr. Robert Ward has been appointed Physician-in-Chief at the Childrens Hospital and Professor and Chairman of the Department of Pediatrics at the University of Southern California School of Medicine. Dr. Ward, presently Professor of Pediatrics at New York University College of Medicine and Visiting Physician at Bellevue Hospital, will assume his new duties on July 1, 1958.

Dr. Amos Christie, head, pediatrics department, Vanderbilt University School of Medicine, Nashville, received the John Phillips Memorial Award at the convention of the American College of Physicians in Atlantic City, April 30, 1958. The award is named in honor of one of the pioneers in the development of internal medicine as a specialty and one of the founders of the college. Dr. Christie was selected for his research work concerning histoplasmosis.

The **Intermountain Pediatric Society** announces its annual meeting, to be held at Sun Valley, Idaho, July 4, 5, and 6, 1958.

Guest speakers include Robert Gross, M.D., Sam Levine, M.D., Lawson Wilkins, M.D., Astley A. Weech, M.D., and Russel Blattner, M.D.

For further information write to Thales H. Smith, M.D., 220 North University Avenue, Provo, Utah, Secretary Intermountain Pediatric Society.

Pergamon Institute, a non-profit foundation, has recently been formed in Washington, D. C., and is in course of formation in London, for the purpose of making available to English-speaking scientists, doctors, and engineers (from all countries that are members of the United Nations), the results of scientific, technological, and medical research and development in the Soviet Union and other countries in the Soviet orbit.

The International Council of Scientific Unions, during the recent meeting of its Executive Board in Brussels, decided to include a token subvention to the Pergamon Institute in the allocations for 1958, in recognition of the value to international scientific activity of the Aims and Purpose of the Pergamon Institute. Over a hundred scientists of international standing from

many countries have given their support and will supervise the affairs of the Institute.

Discussions are taking place with the relevant authorities in the U. S. S. R. on the commissioning of a series of review volumes, with complete bibliographies, covering broad areas of Russian scientific, medical, and technical progress for the period 1920-1956.

The Institute now publishes a number of selected Russian journals in translation. Those of medical interest are: **Problems of Virology; *Problems of Hematology and Blood Transfusion; *Journal of Microbiology, Epidemiology and Immunobiology; *Problems of Oncology; *The Sechenov Physiological Journal of the U. S. S. R.*

The Institute is also assisting with the translation and publication of important Russian books on medicine which will soon be available in English.

Any doctor wishing to keep informed of what is being published in the U. S. S. R. and other countries in the Soviet orbit may apply to the Institute to receive, free of charge, a monthly contents list in English of all the significant articles and books being currently published in his field of interest in these countries. Persons interested in any article mentioned in these contents lists may order from the Institute a full English translation which will be supplied with a minimum of delay. The charge for such a translation will be on a cooperative cost-sharing basis. This means that the costs will be shared equally with others requesting the article. The costs will be assessed on orders obtained for this translation over a period of six months and the charges to recipients of these papers will be made six months after the first request.

Books

Hormones in Blood. Colloquia on Endocrinology, Volume XI. Ciba Foundation, G. E. W. Wolstenholme and E. C. P. Millar, Editors. Boston, 1957, Little, Brown & Co., 416 pages. Price $9.00.

This volume represents the proceedings of the forty-third international conference held by the Ciba Foundation since 1950 and the seventeenth relating to endocrinology. The keynote of the symposium, "Back to Blood," is more than amply represented by the contributions of scientists from Great Britain, the United States, South America, Sweden, and The Netherlands.

A large portion of the text is concerned with the technological aspects of measuring various hormones in blood, ranging from the protein secretions of the hypophysis to the simpler steroidal and catechol compounds of the gonads and adrenals. Some problems relating to the insensitivity of certain assays for the very small amounts of the hormones in blood, specificity and precision, are thoroughly considered; these basic deliberations should stimulate improvements which may produce the "ordinary" means of estimating ACTH, growth hormone, and gonadotropins. The future may bring about the better understanding of the endocrinologic mechanisms relating to growth and development in man.

Inestimable is the value herein to the physician engaged in endocrinologic research. The book does not purpose to serve as a guide to clinical endocrinology and professes no utility in the practical problems of pediatrics. However, it will bring enlightenment in basic endocrinology to the interested reader.

A few matters relating to pediatrics merit specific mention. The thyroid hormones in blood, with particular reference to pregnancy, are discussed by Pitt-Rivers. After the first month of conception in man, the serum PBI rises, out of proportion to the anticipated calorigenic action on the mother, suggesting an altered utilization of thyroid hormone. The elevation appears to be related to increased thyroxine-binding capacity of the serum and correlated with the higher levels of estrogens. Insulin in blood is given thoughtful consideration by Randle: using the rat diaphragm method, increased levels are described in association with islet cell

*These have financial assistance from the National Institute of Health, United States Department of Health.

tumors of the pancreas—the levels are normal in functional hypoglycemia, but may be "enhanced in some cases of familial hypoglycemia in children." A readily available technique for the assay of insulin would be welcomed for the study of hypoglycemia in childhood. Sayers, in an excellent discussion, presents evidence for mechanisms (possibly neural) other than a "feedback" for the increase in ACTH following noxious stimuli. Many helpful technical suggestions are to be found in Savard's chapter on the steroids in human blood. Employing tritiated aldosterone, Ayres and co-workers estimate the daily production of this important mineral-corticoid to be 170 to 190 micrograms per day on a normal diet, and 780 micrograms on a diet low in salt. Migeon, in an extension of his studies, finds the elevated 17-hydroxycorticosteroids in late pregnancy to be related to a disturbance in disposition rather than increased production by the adrenal cortex; in addition, such steroids are found to cross the placental barrier, with the ratio of the concentration in maternal/cord blood of 2.3-4.7. Von Euler describes methods and compounds pertaining to the catecholamines in blood.

Many other themes of great research interest are included. The editors are to be congratulated for their labors, particularly in connection with the sequelae to each chapter. The discussions appended to each presentation, in which several members of the symposium participate, are as rewarding as the body of the text.

Throughout, the style is direct, clear, ungarnished, and well suited to the aim and facile perusal of the book. The reader will be grateful for the numerous tables and charts. All chapters are moderately well (but not completely) annotated with pertinent references. Finally, a subject index is included, which helps locate specific information, otherwise buried under uncertain chapter headings; this commendable feature is all too often neglected in volumes of this nature.

A. M. B.

The Practice of Infectious Diseases. Louis Weinstein, M.D., New York, 1958, McGraw-Hill Book Co., Inc., 501 pages. Price $8.50.

The treatment of the infectious diseases has been undergoing constant change in recent years as a result of the never-ending procession of new chemical drugs and antibiotics. Dr. Weinstein, in this book intended for the practitioner, presents current knowledge and thinking. There is an excellent introductory chapter on the principles of treatment, which summarizes the specific use of the various drugs, followed by a discussion of the principles of prevention. Then comes the discussion of the specific diseases, which the reviewer found a little confusing due to the unusual classification or arrangement used by the author. They are grouped by anatomic systems, rather than by cause, as viral or bacterial. Thus, mumps is in an early chapter on infections of the mouth and salivary glands, pertussis in the chapter on infections of the lower respiratory tract, and measles in a late chapter on systemic infections with primary manifestations in the skin. That the *primary* manifestations of measles occur in the skin is open to argument. Why not include it on this basis in the chapter on the mouth or upper respiratory tract? (Incidentally there was some difficulty in finding measles, as it is incorrectly indexed as to page.) This unusual arrangement of the diseases is not so important. What is important is that these discussions are excellent and clear. Intentionally rare and uncommon infectious diseases in the United States, such as the tropical group, have not been included. Emphasis is placed on prevention. All in all, it is a sound book for the practitioner for whom it is written and will help him in keeping abreast of the treatment of choice of today. What the treatment of the infectious diseases may be a few years hence is another matter.

Parent-Child Tensions. B. E. Schwarz and B. A. Ruggieri, Philadelphia, 1958, J. B. Lippincott Company, 238 pages. Price $4.95.

A psychiatrist and pediatrician have collaborated to explain to parents the reasons for parent-child tensions. The authors voice a naive faith in the "extreme value not only in the physician's treatment of these disorders but also in the prevention of emotional disturbances," a faith which is not justified by the data. The book, based on the thesis that the "specific feelings and behavior of the child are dependent on the specific feelings and behavior of the parent,"

thereby implying, to the parent at any rate, that unhappiness and misbehavior are the parent's fault, can hardly be expected to allay the feelings of guilt which haunt parents in this psychiatrically minded age.

Bed-wetting is presented as "rarely due to factors other than emotional." The authors regard an unnaturally close relationship between mother and son as a frequent occurrence in cases of bed-wetting in boys. In girls who wet, the "fundamental problem is also frequently an emotional conflict stemming from the girl's sleeping in the same bedroom with her parents, but, in the girl's case, it is her father who is unnaturally close to her."

The various conditions are presented in the form of case narratives. Parents will find little to comfort or accurately inform them in this book.

Pediatric Index. A Guide to Symptomatological Diagnosis and Current Management. Edwin F. Patton, M.D., St. Louis, 1958, The C. V. Mosby Co., 639 pages. Price $13.50.

This is a unique book. It may be described as a kind of pediatric diagnostic *vade mecum*. In a first section of over 300 pages the author lists presenting symptoms and physical signs in alphabetical order either under their own name or part of body affected, and tentative diagnoses. These further are subgrouped under each heading according to whether characteristic of the newly born infant, the infant from 2 weeks to 2 years of age, or the child of any age. Finding the condition or conditions which best fit the clinical picture, the reader then turns to Section II (300 pages) where the definitive dingnoses are discussed together with the treatment. These also are arranged in alphabetical order. A third short section presents special data, and a number of techniques applicable to the treatment of a number of conditions such as "electrolyte and fluid adjustment." It is not a book intended to be carried in the bag for quick reference, like Davidson's *Compleat Pediatrican*, which it resembles somewhat in scope although the approach and arrangement of the material are quite different, nor does it resemble in any way the usual pediatric textbook. Its preparation was obviously a monumental task, and the publisher has brought it out in an excellent format with clear, legible type. It is distinctly a book for the practitioner, but should be a most useful volume for the hospital and resident staff library. It is really something different in pediatric texts.

Tracheotomy: A Clinical and Experimental Study. Thomas G. Nelson, M.D., Baltimore, 1958, Williams & Wilkins Co., 111 pages. Price $3.75.

A monograph by Major Nelson of the M.C., U.S.A.R., based on a study of 300 tracheotomies at Brooke Army Hospital. The monograph begins with an interesting history of tracheotomy. This is followed by a discussion of the clinical material, the operative techniques, and the care of the patient with a tracheotomy. Next comes an Experimental Section in which the author presents his studies of the healing of the wound. Dr. Nelson considers tracheotomy as a singularly safe and efficient means of saving life, which simplifies the management of a wide range of common diseases and accidents. He considers the measure as having saved the lives of one-fourth of the 300 patients in the clinical study.

Lehrbuch der Kinderchirurgie. Priv.-Doz. Dr. M. Grob, Zurich, with the collaboration of Dr. M. Stockmann, Lucerne, and Dr. M. Bettex, Zurich, Stuttgart, 1957, Georg Thieme Verlag, 775 pages, 876 illustrations. Price DM157. In USA and Canada: Intercontinental Medical Book Corporation, New York 16, N. Y. Price $37.40.

A new textbook on pediatric surgery comes from the Pediatric Clinic of the University of Zurich; its author is the head of its surgical department, Dr. Max Grob.

After an introductory chapter on preoperative care, anesthesia, water and electrolyte balance, chemotherapeutic and antibiotic drugs, postoperative care and "hibernation" (the latter comprising not only hypothermia in anesthesia, but also long-term induced depression of vital processes by drugs, "lytic cocktail"), there are chapters on the surgery of the cranium and its

contents, on maxillofacial surgery including plastic surgery of the face, on surgical diseases of the neck, throat, and larynx, of the chest (including about 100 pages on cardiac surgery), surgery of the abdomen, of the urinary tract and the male and female genital tracts and the retroperitoneum, some surgical conditions of the spine, surgical diseases of skin and soft tissue, and of bone and joints, including congenital malformations of the skeleton, numerous other orthopedic conditions, fractures and bone tumors.

This book is of about the same size as its American counterpart, *The Surgery of Infancy and Childhood*, by Robert E. Gross; it covers a considerably larger field, reaching, as shown above, into many areas of special surgery; naturally, its treatment of the single subjects is shorter and result statistics less specific than those of Gross's book. One gains the impression that the material of the Zurich Clinic is smaller than that of the Boston Children's Hospital.

This book has many well-reproduced photographs, roentgen pictures, and a few line drawings of operations. It is writen in an easy-to-read and clear German.

By and large, German-Swiss pediatric surgery, as reflected in this book, follows the same principles and practices as that in the United States, although in some instances Dr. Grob's opinion and procedure differ from our prevailing practice. This book is the first comprehensive work on pediatric surgery in German for more than two decades; it should be of much help to surgeons in German-speaking countries. For the American surgeon it may be of some value in the areas not covered by the above-mentioned American book on pediatric surgery, and because of the occasional divergences between the practice in this country and abroad, especially in questions still controversial in the United States.

H. L.

Principal Infectious Diseases of Childhood. Nelles Silverthorne, M.B., Toronto, 1958, University of Toronto Press, 102 pages. Price $3.50.

A small manual for the medical student and practitioner. The discussions are rather sketchy as the author attempts to cover 50 topics in a hundred pages. For some reason there is little discussion of the prevention of the communicable diseases of childhood. For example, while a page is given to the detailed treatment of a patient with diphtheria, prevention is dismissed with the statement: "Prophylactic: the general use of diphtheria toxoid in children prevents its occurrence."

A Mental Health Handbook. I. Skottowe, London, 1957, Edward Arnold & Co., 196 pages. Price $5.50.

In this book, Skottowe presents an excellent brief survey of mental health problems. Though the book is designed primarily for social workers and other health workers, it contains much that will benefit the physician. Special attention is paid to social factors and to the possibility of influencing these by social action.

The point of view is a well-balanced one and the language readily comprehensible.

Cardiovascular Rehabilitation. Paul D. White, M.D., Howard Rusk, M.D., Bryan Williams, M.D., and Philip R. Lee, M.D., New York, 1957, McGraw-Hill Book Co., Inc., 155 pages. Price $6.50.

The report of a conference held at the New York University-Bellevue Medical Center. It presents the problems facing the physician in the rehabilitation of patients with cardiovascular disease. The report is in the form of a discussion, in which many participated, and is of particular interest to those concerned with the general problems of rehabilitation as well as to the cardiologist.

Einführung in die Kinderheilkunde. E. Glanzmann, Vienna, 1958, Springer-Verlag, 1068 pages. Price $17.85.

This fourth edition of the pediatric textbook by Professor Glanzmann of Bern includes many of the changes in pediatric knowledge that have taken place since the previous edition published in 1949. A number of new chapters, or Vorlesungen, have been introduced as "the newer antibiotics" and "Salk vaccine." The text is a standard on the Continent and is written for the student and practitioner. While it is replete

with references by name, there is no bibliography. Those who read German fluently will find it an interesting presentation of Continental pediatric practices.

Management of the Handicapped Child. H. Michal-Smith, Ph.D., Editor, New York, 1957, Grune & Stratton, Inc., 276 pages. Price $6.50.

A collection of 13 discussions by different authors of the problems and management of children with various types of handicaps. Some chapters deal with physical handicaps, such as speech and language, hearing, nephrosis, and neuromuscular, while others are discussions of topics not usually included under the term "handicapped," such as behavior problems, nervous habits, and emotionally deprived children. All of the authors are well-known prominent leaders in their particular fields of interest.

Traumatologie Infantile. P.-L. Chigot and P. Esteve, Paris, 1958, L'Expansion, 358 pages. Price 5,000 frs. (French).

A monograph or text on fractures in childhood, of more interest to the surgeon or orthopedist than the pediatrician. The work is based on the services at the Trousseau Hospital in Paris, and it is excellently illustrated with 114 drawings, photographs, and roentgenograms. It is well recognized that fractures in young children differ in a number of ways from fracture of the same bones in adults, and hence the place for such a text. It is a useful contribution to pediatric surgery.

Microscopic Anatomy of the Temporal Bone. Dorothy Wolff, Ph.D., Richard J. Bellucci, M.D., and Andrew A. Eggston, M.D., Baltimore, 1957, Williams & Wilkins Co., 444 pages. Price $12.50.

A beautifully illustrated and printed monograph by members of the staff of the Manhattan Eye, Ear and Throat Hospital. While undoubtedly of interest and value to otologists by its very subject and nature, it is not a book that will interest pediatricians.

Perception and Cerebral Palsy. William M. Cruickshank, H. V. Bice, and N. E. Wallen, Syracuse, N. Y., Syracuse University Press, 1958, 123 pages. Price $5.00.

A technical report of a study of perceptual performance in a group of children handicapped by cerebral palsy.

Problems of Adolescents. H. Edelston, M.D., D.P.M., New York, 1956, Philosophical Library, 174 pages. Price $4.75.

A discussion of sex education by a psychiatrist, based on his experiments with Youth Clubs. In a series of lectures and group discussions, questions and sex problems raised by the adolescents were discussed.

Current Therapy 1958. Edited by Howard F. Conn, M.D., Philadelphia, 1958, W. B. Saunders Co., 827 pages. Price $12.00.

Many chapters have been rewritten, keeping pace with the rapid advances in therapy resulting from the introduction of new drugs. There are over 250 contributors to the current volume.

Certain Language Skills in Children. Mildred C. Templin, Minneapolis, 1957, University of Minnesota Press, 183 pages. Price $4.00.

A monograph of the Institute of Child Welfare of the University of Minnesota. Of interest to those working with young children in remedial clinics of different types, rather than to the pediatrician in practice.

80 Puerto Rican Families in New York City. Beatrice B. Berle, M.D., New York, 1958, Columbia University Press, 331 pages. Price $4.75.

A sociomedical study of 80 Puerto Rican families which have migrated from the island to New York City. An interesting presentation of the living and health problems of a group which forms an increasing segment of the population of New York.

Diseases of Children. Bruce Williamson, M.D., F.R.C.P. (Lond.), Edinburgh, 1957, E. & S. Livingstone, Ltd., 483 pages.

The eighth edition of Williamson's Handbook first published in 1933.

Editor's Column

EDITOR'S COLUMN

PEDIATRIC PRACTICE AND ITS REWARDS

IN RECENT months the JOURNAL has published a number of letters from its readers on the subject of the rewards, or lack of rewards, of pediatric practice.

Whether a medical career is rewarding depends on a number of factors. Important among these are the personality of the physician, his motivations, his philosophy toward life, and the particular interest developed during his student days which determines the direction of his medical career. There are many paths open in medicine that may be followed, both in practice and in the various fields of medical research. That a few get started on a wrong path is to be expected. This, however, does not mean that the particular field, whether it be in practice or academic work, is not full of rewards for the vast majority who select it. While it is unfortunate when a physician makes a wrong choice and as a result finds himself unhappy and discontented, the fault almost always lies in the individual, and the blame cannot be shifted to the particular field. "Look within thyself when things go wrong," is a wise maxim, even if it is unpleasant to the ego. While the correspondence referred to pediatrics, we have known unhappy individuals in other branches of medical practice, as well as in academic and research work. Some would have been unhappy and discontented no matter what field they had selected.

The correspondence, however, raises an important question involving pediatrics to which both the older and younger participants call attention. Essentially the question is whether the specialized training in pediatrics of the hospital residency of today prepares the young pediatrician to understand and cope with the problems he will meet in pediatric practice. It is in private practice, not academic pediatrics or research, that the vast majority of pediatricians will spend their life. Those in charge of the graduate teaching of pediatrics in academic departments and children's hospitals have a definite obligation to prepare the residents for pediatric practice. The question that has been raised is by no means new, and we are familiar with a number of academic departments concerned with the problem and with the measures taken to try and find a solution. The problem has resulted in part from the change in the type and character of the diseases for which children are admitted to the hospital wards. This has been brought about by the strides that have taken place in therapeutics and preventive medicine

in recent years. Their effect has been even more striking in what constitutes a pediatric practice today, and only the "old-timer" fully appreciates the extent of this change. No small part of the present-day hospital admissions consist of rare and unusual conditions sent in for study and treatment. These are culled from hundreds of private practices, and many of the conditions will never, or only a few times, be seen in an average lifelong private practice. The problem develops from the resident spending so much of his training time in the study of these unusual and "interesting" cases that he gains the impression that this is what the practice of pediatrics consists of. If this happens he has a rough awakening in store for him when he enters practice.

There has been an increasing awareness by many hospitals and academic departments of the importance of including opportunities in the training program for the resident to become familiar with the type of work he will be occupied with in practice. The programs so far developed are not clear-cut and are experimental. There is general agreement on experience in the infant welfare center for the feeding and supervision of normal babies. Ample time for work in the outpatient service is also considered important. In addition, some send the resident for a period to hospitals in smaller cities, and others are experimenting with sending the resident for a month to a private pediatric clinic. A number of medical schools in recent years have been experimenting with placing the undergraduate medical student with a practitioner for a period, a return to the "preceptor" method of medical education.* In addition, many hospitals are developing the psychologic study of the hospitalized children and their family interrelationships, but there is no agreement as to the best method of interesting and involving the resident in this important facet of his future pediatric practice. Some academic departments are so imbued with the idea that research is the all-important function of the hospital service that they feel such broadening of the residency training will interfere with the scientific program. It is this group in particular that should ponder over the correspondence. We have no thought of minimizing the importance of scientific research in pediatrics, as it is the basis of progress, but we cling to the idea that the care of the patient is the primary function of the physician and hospital. Incidentally, from years of close acquaintanceship with both groups, we would venture there is as high a proportion of discontented individuals in academic work as in practice.

The importance of the correspondence lies in the fact that it expresses the viewpoint of a group of practitioners based on their experience, which they sometimes find difficulty in obtaining the opportunity to express. These are the men and women who bring the "healing art" to people in their time of trouble and need, and this is the primary purpose of medicine as a profession. It stands out clearly in the discussions that a physician in pediatric practice must have a deep love for children as individuals, if he is to be happy, contented, and successful.

*A discussion of the pros and cons of the extramural preceptorship may be found in the April 3, 1958, issue of the *New England Journal of Medicine*, page 691.

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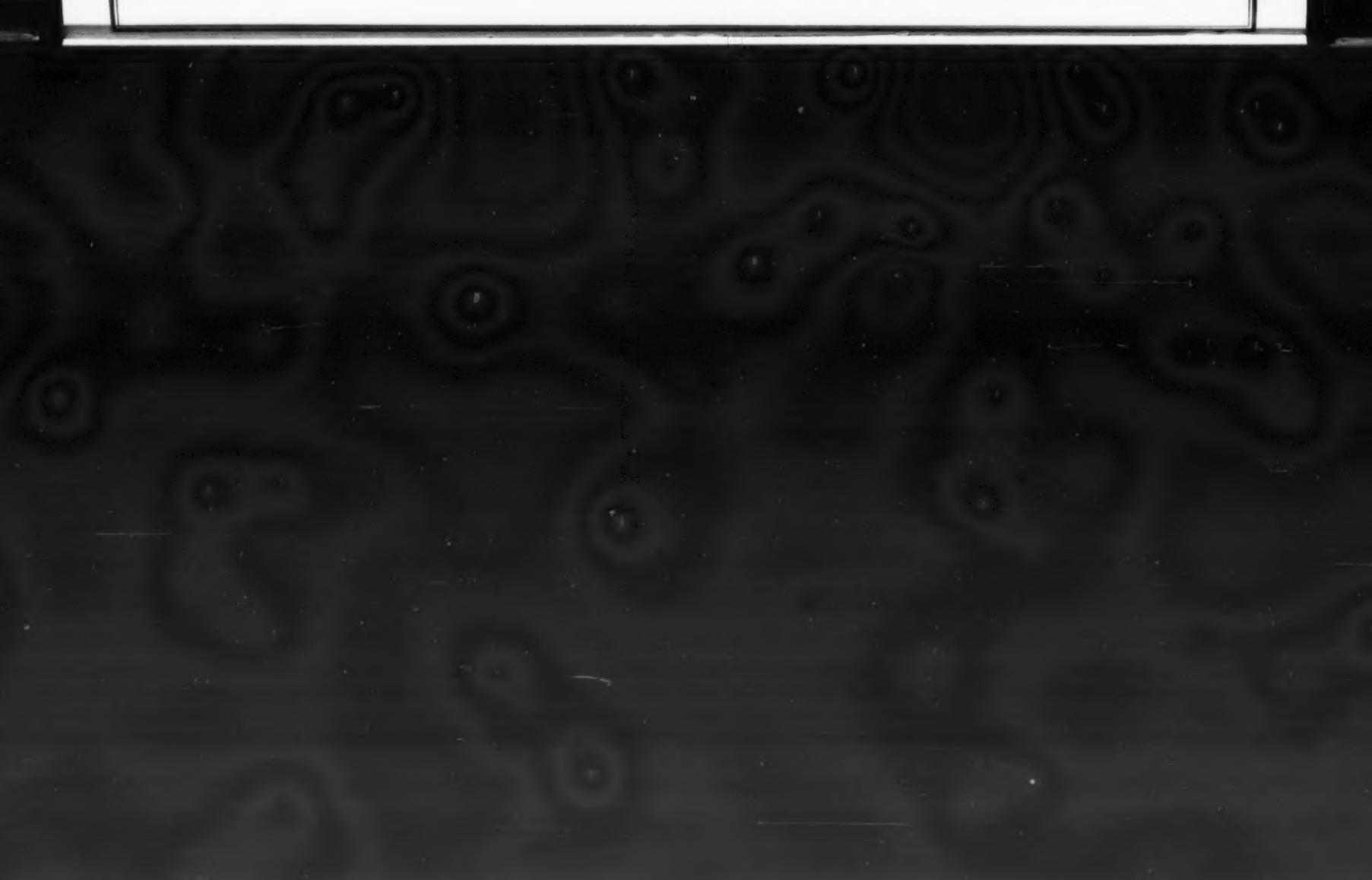

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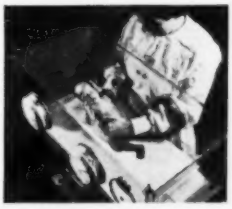

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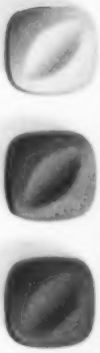

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1 or 2 capsules daily, or as recommended by a physician.

Bottles of 30 and 100.

new, improved
THERAGRAN

Theragran—the original and most widely prescribed therapeutic vitamin preparation—is now expanded to include vitamin B_{12}, pyridoxine and d-calcium pantothenate . . . providing extra nutritional value at no extra cost to your patients.

also available
THERAGRAN LIQUID
for patients who prefer liquid vitamin therapy

THERAGRAN-M
with extra vitamins and minerals

"THERAGRAN" IS A SQUIBB TRADEMARK

SQUIBB

pamper

BABY'S SENSITIVE SKIN
with the
TENDER, LOVING CARE
of

DESITIN®

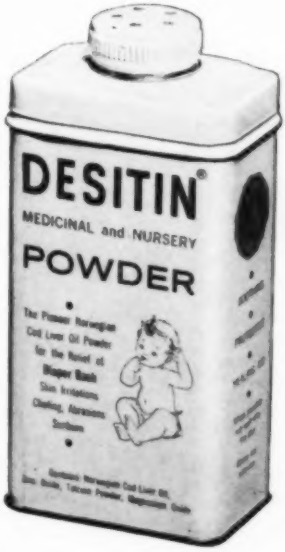
Medicinal and Nursery

POWDER

soothing, lubricating, protective and *healing* in

DIAPER RASH

prickly heat rash
chafing, skin irritations



the original and *only* baby powder saturated with Norwegian Cod Liver Oil (plus its vitamins A and D) — so will not deprive the skin of its natural fats.

DESITIN POWDER works hand in hand with DESITIN OINTMENT to help keep baby's skin smooth, supple, free from diaper rash, excoriation and chafing. Why not recommend both DESITIN POWDER and DESITIN OINTMENT.

samples
on
request

DESITIN CHEMICAL COMPANY
812 Branch Ave., Providence 4, R. I.

for diarrhea

LACTINEX

TABLETS & GRANULES

LACTINEX GRANULES and LACTINEX TABLETS contain a standardized viable mixed culture of Lactobacilli acidophilus and bulgaricus with the naturally-occurring metabolic enzymes produced by these organisms.

LACTINEX TABLETS—A clinically proven treatment for gastro-intestinal disturbances, including diarrhea[1,2,3] (antibiotic induced and others) in infants and adults.

LACTINEX GRANULES—An especially designed dosage form (served on cereal, food or with milk) of this effective product for the pediatric and geriatric patient.

Dosage: Three or four tablets or one packet, three or four times a day.

Supplied—tablets in bottles of fifty—granules in boxes of twelve, one gram packets.

1. Siver, Robert H.: Current Medical Digest, Vol. XXI, No. 9, September 1954.
2. McGivney, John: Texas State Journal of Medicine, Vol. 51, No. 1, January 1955.
3. Frykman, Howard M.: Minnesota Medicine, Vol. 38, No. 1, January 1955.

HYNSON, WESTCOTT & DUNNING, INC., Baltimore 1, Md.

For thorough Vitamin Support

BUILDS SOUND BODIES DURING
CRITICAL FORMATIVE YEARS

PLURAVIT® DROPS

a pleasant lime flavored, readily dispersible combination of 8 essential vitamins

Each 0.6 cc. contains:

Vitamin A	5000 units
Vitamin D_2	1000 units
Vitamin B_1	1 mg.
Vitamin B_2	0.4 mg.
Vitamin B_6	1 mg.
Nicotinamide	5 mg.
Pantothenic acid	2 mg.
Vitamin C	50 mg.

Stable • Mixes Readily

DOSAGE: Infants 0.3 cc., children and adults 0.6 cc. daily. May be taken directly or stirred in milk, fruit juices, or other food.

HOW SUPPLIED: Bottles of 15 and 50 cc. with graduated dropper.

Winthrop LABORATORIES
NEW YORK 18, N. Y.

Pluravit, trademark reg. U. S. Pat. Off.

for Strategic Nutrition

in Pediatrics

Whether meals must be planned for weight-losing, weight-gaining, or just for normal day-to-day growth-promoting nutrition . . .

Enriched Bread

with its growth-applicable protein, available energy, B vitamins, iron and calcium, has a well-justified place in every meal.

Because it is also an excellent vehicle for other foods, it fills an especially strategic position at snacktime.

AMERICAN BAKERS ASSOCIATION

20 North Wacker Drive Chicago 6, Illinois

PROTECTION AGAINST SKIN IRRITATIONS

cleanses, lubricates, soothes delicate skin... combats infections

Johnson's Baby Lotion forms a discontinuous film—not an impenetrable barrier—to more effectively minimize skin irritations.

- low surface tension readily permits contact of soothing lanolin with the skin—enhances antibacterial action of hexachlorophene
- lets skin function normally—heat and perspiration escape readily
- combats miliaria, other irritations

Contains hexachlorophene, 0.5 per cent.

bettering baby care through specialized research

BABY PRODUCTS DIVISION

Johnson & Johnson

to prevent
vertigo
nausea
vomiting
as in
motion
sickness

before the motion upset starts **BONAMINE***

brand of meclizine hydrochloride

No other therapy can compare to the single-dose, 24-hour effectiveness,[1] safety and acceptability of BONAMINE for children. Protection includes the frank manifestations as well as the disturbing earlier symptoms of apathy, indifference, petulance, anorexia, sleepiness, and/or headache, etc. Side effects are extremely rare—"less than in the case of the other agents"[2]—and usually minor and transient when encountered.

Also indicated for vertigo, nausea, vomiting in: common pediatric infections • postoperative patients • opiate or other drug therapy • radiation therapy, fenestration procedures, labyrinthitis

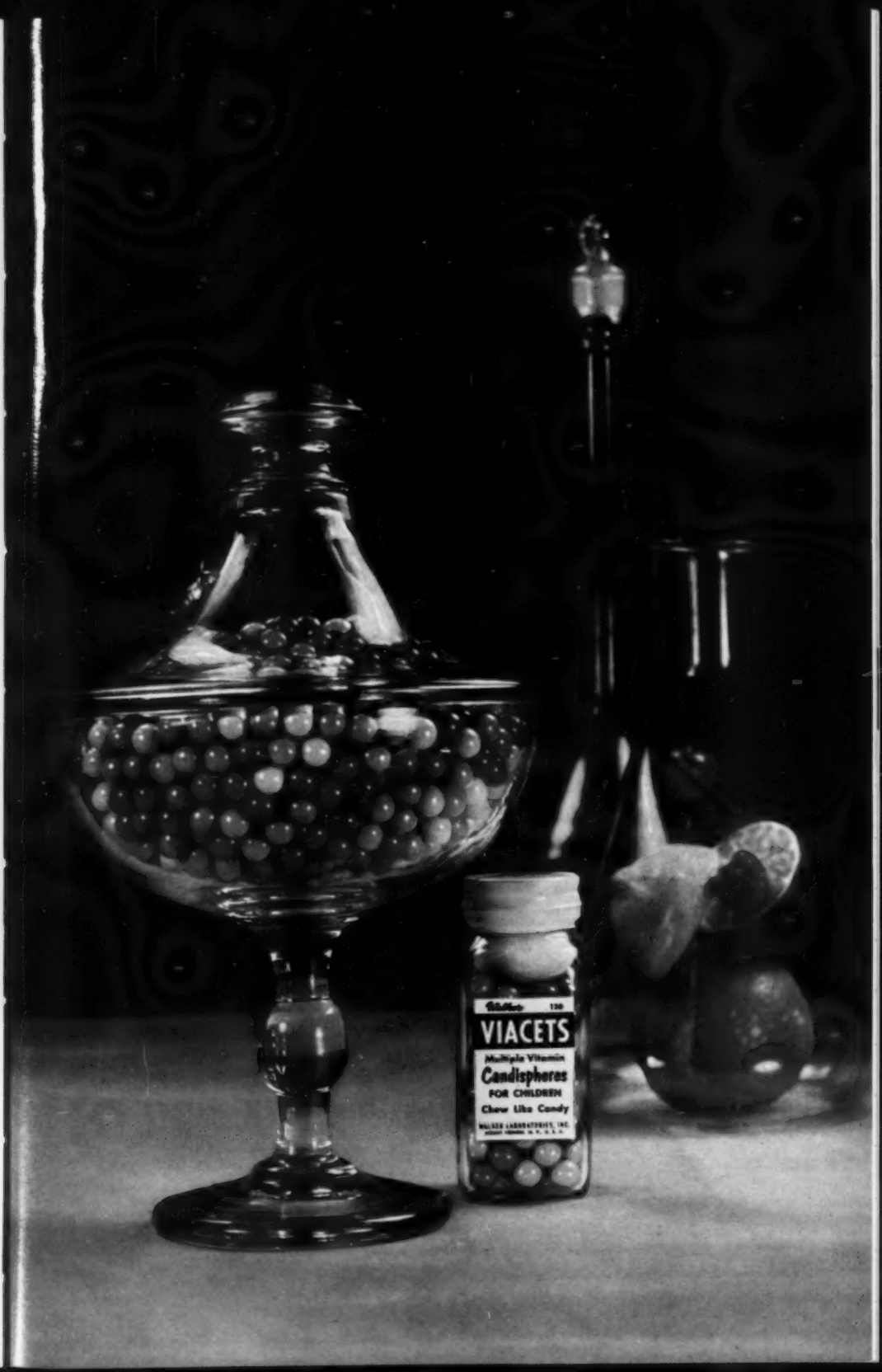
BONAMINE Tablets, scored, tasteless, 25 mg. Boxes of 8, bottles of 100 and 500.

BONAMINE Chewing Tablets, pleasantly mint flavored, 25 mg. Packages of 8.

1. Report of Study by Army, Navy, Air Force Motion Sickness Team: J.A.M.A. 160:755, 1956. 2. Moyer, J. H.: M. Clin. North America, March, 1957, p. 405.

*Trademark

PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York Pfizer


VIACETS
Multiple Vitamin
Candispheres
FOR CHILDREN
Chew Like Candy

VIACETS
Multiple Vitamin
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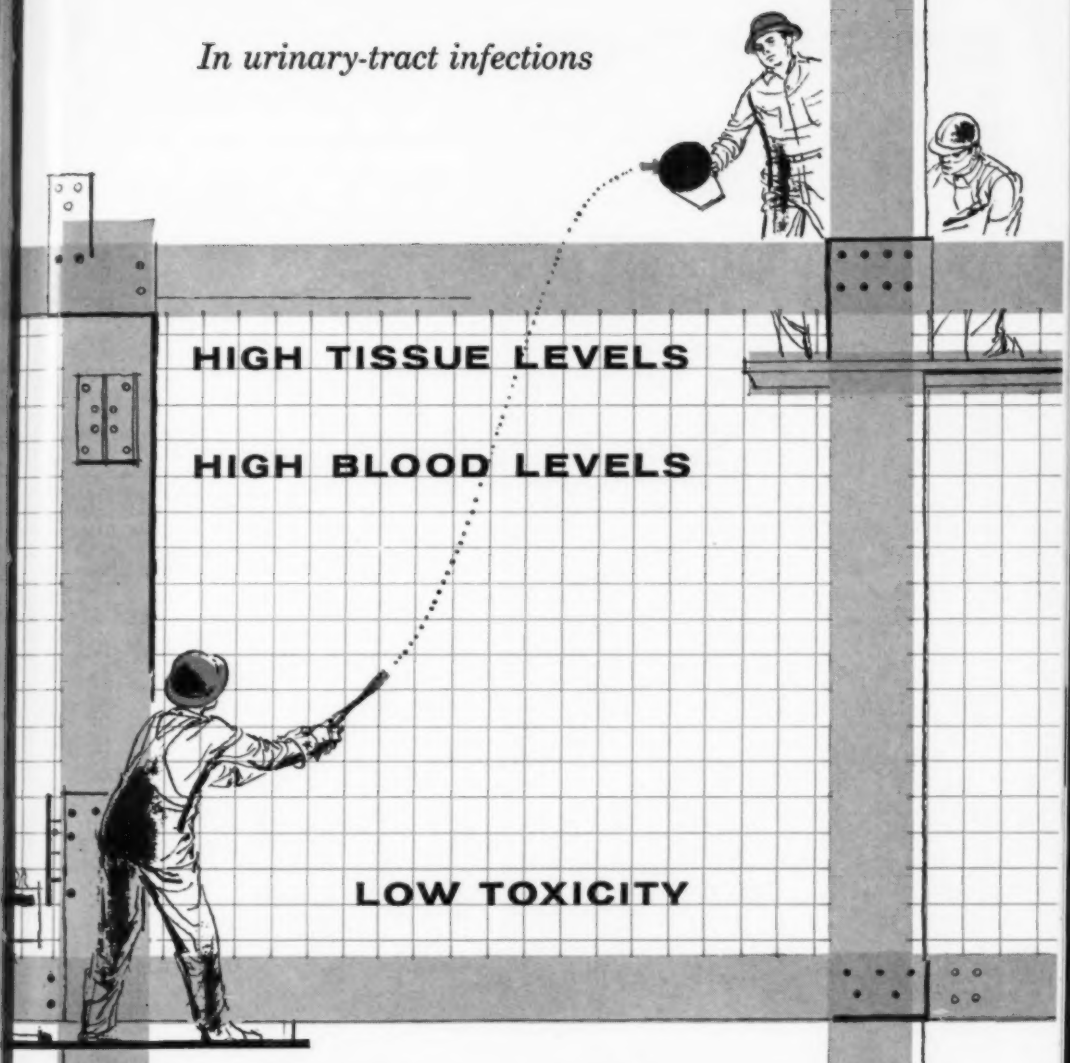
FOR CHILDREN
Chew Like Candy

In urinary-tract infections



HIGH TISSUE LEVELS

HIGH BLOOD LEVELS

LOW TOXICITY

SUSPENSION **TABLETS**

SULFOSE®

Triple Sulfonamides, Wyeth
(*Trisulfapyrimidines: Sulfadiazine, Sulfamerazine, Sulfamethazine*)

PHYSICIANS' COUNCIL · INFORMATION ON CHILD HEALTH ·

This advertisement conforms to the Code for Advertising of the Physicians' Council for Information on Child Health.

Wyeth®
Philadelphia 1, Pa.

# of infant feeding

Standard formulas for WELL INFANTS

Since age, appetite and digestive capacity vary, hospital practice favors an individualized formula for each infant.

The total daily feeding usually amounts to 2 ounces of milk *per pound of body weight*, plus 1 ounce of Karo Syrup with enough water to satisfy fluid requirements.

The newborn usually takes from 2 to 3 ounces of formula per feeding; the very young infant, 4 to 5 ounces—the daily quota yielding over 50 calories for each pound the infant weighs. The quantity per feeding should not exceed 8 ounces.

Newborns are fed at 3 to 4 hour intervals throughout the 24-hour period—the 2 or 3 A.M. feeding is discontinued after the neonatal period. In the third or fourth month the 10 or 12 P.M. feeding is discontinued, once the infant fails to awaken for the bottle. Standard but individualized formulas which constitute the hospital infant feeding regimen are shown here.

WHOLE MILK FORMULAS

Age Months	Cow's Milk Fluid Oz.	Water Oz.	KARO Tbsp.	Each Feeding Oz.	Feedings in 24 Hrs.	Total Calories
Birth	10	10	2	3	6	320
1	12	13	2½	4	6	390
2	15	13	3	4½	6	480
3	17	9	3	5	5	520
4	20	11	3½	6	5	610
5	23	11	4	6½	5	700
6	26	10	4	7	5	760

EVAPORATED MILK FORMULAS

Age Months	Evap. Milk Fluid Oz.	Water Oz.	KARO Tbsp.	Each Feeding Oz.	Feedings in 24 Hrs.	Total Calories
Birth	6	12	2	3	6	380
1	8	16	3	4	6	532
2	9	14	3	4½	5	576
3	10	15	3½	5	5	650
4	12	18	4	6	5	768
5	12	21	4	6½	5	768
6	13	22	4	7	5	768

ADVANTAGES OF KARO® IN INFANT FEEDING

Composition: Karo Syrup is a superior dextrin-maltose-dextrose mixture because the dextrins are nonfermentable and the maltose is rapidly transformed into dextrose which requires no digestion.

Concentration: Volume for volume Karo Syrup furnishes twice as many calories as similar milk modifiers in powdered form.

Purity: Karo Syrup is processed at sterilizing temperatures, sealed for complete hygienic protection and devoid of pathogenic organisms.

Low Cost: Karo Syrup costs 1/5 as much as expensive milk modifiers and is available at all food stores.

Free to Physicians—Book of Infant Feeding Formulas with convenient schedule pads. Write:

Medical Division
CORN PRODUCTS REFINING COMPANY
17 Battery Place, New York 4, N.Y.

For Ample Air Right Now!

in Asthma

and other Allergic States

Medihaler-EPI®

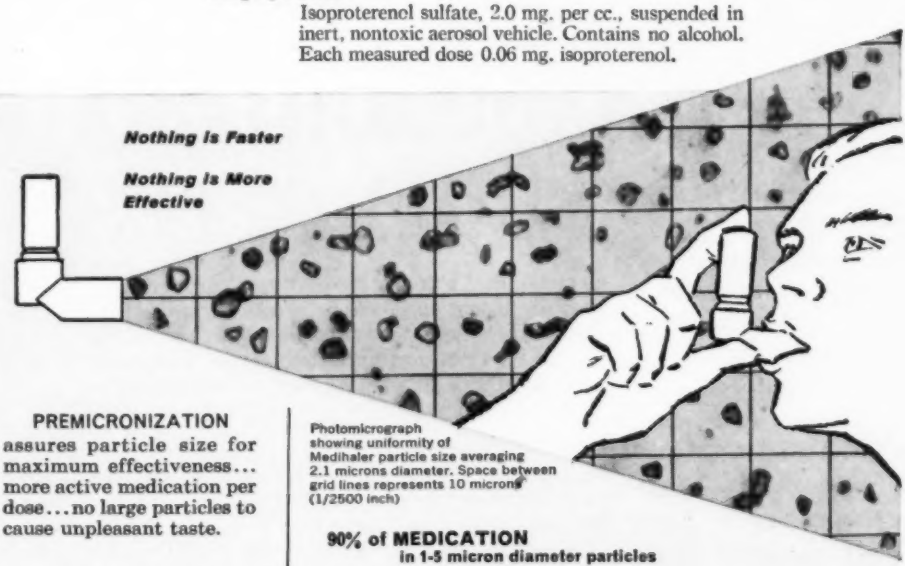
For quick relief of bronchospasm of any origin. More rapid than injected epinephrine in acute allergic attacks.

Epinephrine bitartrate, 7.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose 0.15 mg. epinephrine.

Medihaler-ISO®

Unsurpassed for rapid relief of symptoms of asthma and emphysema.

Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose 0.06 mg. isoproterenol.



PREMICRONIZATION assures particle size for maximum effectiveness... more active medication per dose... no large particles to cause unpleasant taste.

THE MEDIHALER® PRINCIPLE means automatically measured-dose aerosol medications in spill-proof, leakproof, shatter-proof, vest-pocket size dispensers.

Photomicrograph showing uniformity of Medihaler particle size averaging 2.1 microns diameter. Space between grid lines represents 10 microns (1/2500 inch)

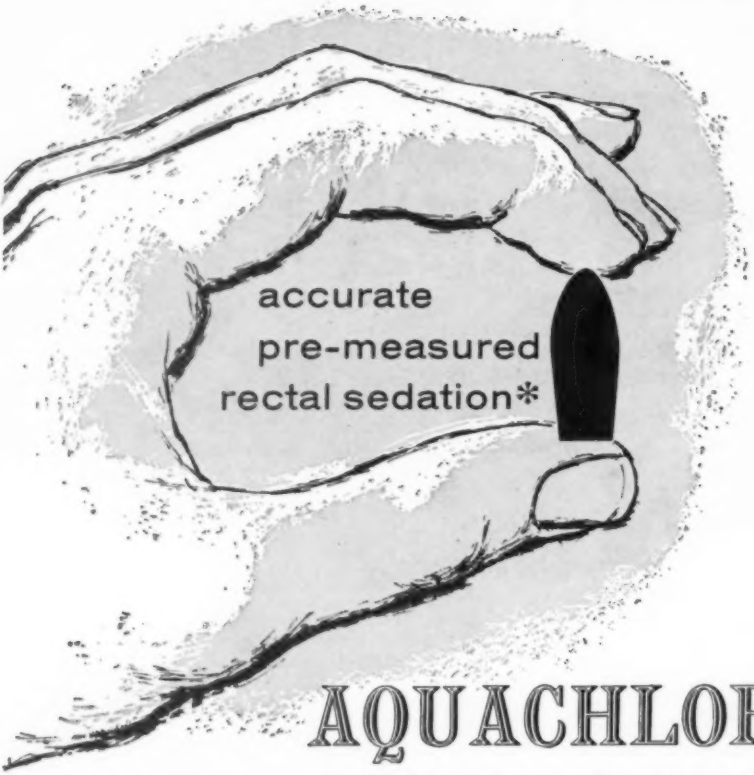
90% of MEDICATION in 1-5 micron diameter particles

99.9% of PARTICLES in 1-7 micron diameter range

New Improved Premicronized Medihaler suspension ...55 mcg. drug/dose 1-5 microns range

Old type aerosol solution.....	10-12 mcg. drug/dose 1-5 microns range
Squeeze bulb nebulizers.....	2-3 mcg. drug/dose 1-5 microns range

Riker
LOS ANGELES



AQUACHLORAL® SUPPRETTES®

CHLORAL HYDRATE
Rectally
SAFE SEDATION
WITHOUT HANGOVER

- Whenever oral therapy is difficult or impossible
- In nausea and vomiting
- To control convulsions
- To quiet hyperexcitability
- Preoperatively
- Postoperatively

The "Neocera" Base
Makes the Difference

Contains no oils or fatty materials. Consists of water-soluble Carbowaxes* with active dispersal agent.
*Trademark U.C.C.

Aquachloral Suppettes give *total* drug release within 10 minutes after insertion for prompt sedation. Sedation is accomplished free of gastric or rectal irritation and barbiturate hangover. Rectal administration of Suppettes minimizes careless and excessive use. Dosage is non-cumulative.

Composition: Aquachloral Suppettes contain chloral hydrate in three dosage forms: 5 gr. (0.3 Gm.); 10 gr. (0.6 Gm.); 15 gr. (1.0 Gm.), in Webster's exclusive water-soluble "Neocera" dispersal base.

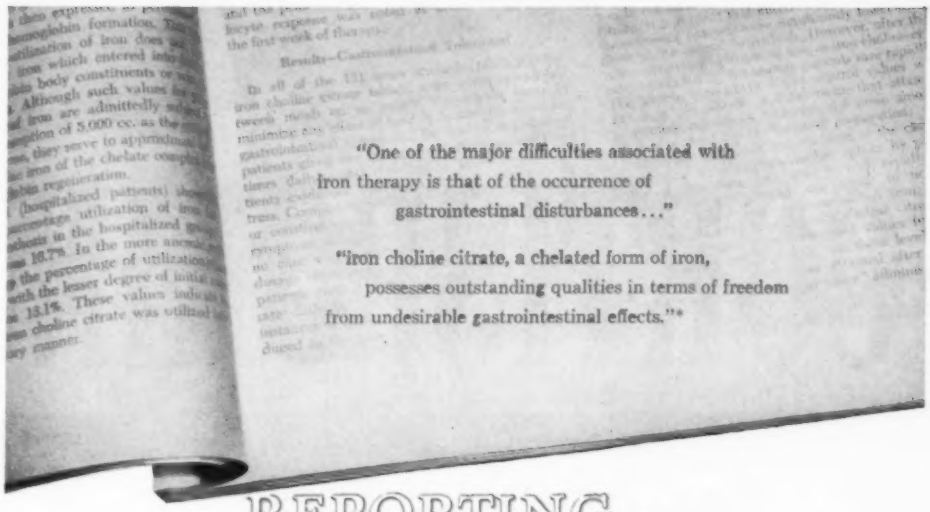
Supplied: In jars of 12.

Administration and Dosage: Rectally. *Children:* Under 2 years, 0.2 to 0.5 Gm.; 2–6 years, 0.5 to 1.0 Gm.; 6–12 years, 1.0 to 1.3 Gm. *Adults:* 0.6 to 1.2 Gm., as needed.

NO REFRIGERATION NECESSARY

SAMPLES ON REQUEST

Webster **THE WILLIAM A. WEBSTER COMPANY • MEMPHIS 5, TENNESSEE**


"One of the major difficulties associated with
iron therapy is that of the occurrence of
gastrointestinal disturbances..."
"iron choline citrate, a chelated form of iron,
possesses outstanding qualities in terms of freedom
from undesirable gastrointestinal effects."*

REPORTING...

new freedom from g.i. distress in oral iron therapy—through the chemistry of chelation

chelate iron therapy with*

FERROLIP® Pediatric Drops

(Iron Choline Citrate)

the new chemohematinic for oral iron therapy... notably effective... exceptionally well tolerated... unusually safe even on accidental overdosage

PEDIATRIC DROPS—Each cc. FERROLIP Pediatric Drops provides 16 mg. elemental iron, 48 mg. choline base. In 30-cc. unbreakable plastic squeeze bottles.

TABLETS—3 FERROLIP Tablets supply 1.0 Gm. iron choline citrate,† equiv. 120 mg. elemental iron, 360 mg. choline base. Bottles of 100, 1000.

SYRUP—1 fl.oz. FERROLIP Syrup provides 120 mg. elemental iron, equiv. 3 tablets. Pints, gallons.

also available

FERROLIP ob *during pregnancy*—Bottles of 60, 100, 1000 tablets.

FERROLIP plus *for macrocytic and microcytic anemias*
Bottles of 100, 1000 capsules. Also FERROLIP plus Liquid, in 8-fl.oz., pint, and gallon bottles.

Flint, EATON & COMPANY
Decatur, Illinois

*Franklin, M., et al.: Chelate Iron Therapy, J.A.M.A. 166:1685, Apr. 5, 1958.
†U.S. Pat. 2,575,611

anti-inflammatory.... bactericidal

'CORTISPORIN'®

For infected, or potentially infected, inflammatory conditions of the eye (anterior segment), ear and skin

VIRTUALLY NON-SENSITIZING

'CORTISPORIN' brand OINTMENT

Each Gm. contains: 'Aerosporin'® Sulfate Polymyxin B Sulfate 5,000 Units; Bacitracin 400 Units; Neomycin Sulfate 5 mg.; Hydrocortisone (free alcohol) 10 mg. (1%).

Available in applicator tip tubes of ⅛ oz. and ½ oz.

'CORTISPORIN' brand OTIC DROPS

Each cc. contains: 'Aerosporin'® Sulfate Polymyxin B Sulfate 10,000 Units; Neomycin Sulfate 5 mg.; Hydrocortisone (free alcohol) 10 mg. (1%).

Available in sterile dropper bottles of 5 cc.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

Kanana Banana Flakes for *instant* mashed banana in daily routine feeding!

• ***PURE*** • ***PERFECTLY RIPE***
• ***FULLY NUTRITIOUS***

The addition of three parts water or milk will INSTANTLY provide the wholly-nutritious mashed banana you prescribe.

When you prescribe banana, write "Kanana"!

Kanana Banana Flakes (NOT A POWDER)

FREE SAMPLE! Fill out and mail TODAY! For content analysis and free sample, send to:

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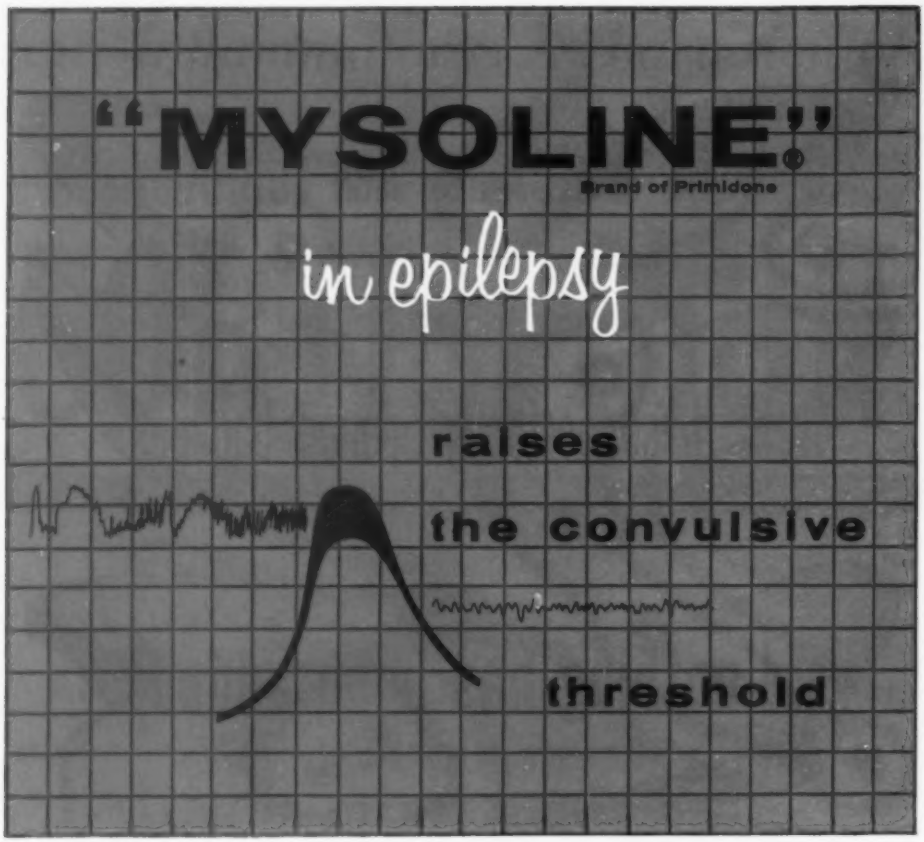

Over 100 investigators in 15 countries have clinically demonstrated that "Mysoline"—alone or in combination with other anticonvulsants — effectively controls grand mal and psychomotor attacks with a high degree of safety. No irreversible toxic effects have been reported. This is now supported by three years of successful clinical use in the United States.

Supplied: 0.25 Gm. scored tablets, bottles of 100 and 1,000.

Ayerst AYERST LABORATORIES • NEW YORK, N. Y. • MONTREAL, CANADA

"Mysoline" is available in the United States by arrangement with Imperial Chemical Industries Ltd.

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YOU'RE THE DOCTOR

With Lipo Gantrisin, *you* control administration — specifying two, four or six doses per 24 hours, as you think best. Lipo Gantrisin permits such flexibility because it provides both prompt and prolonged absorption, giving therapeutic blood levels for up to 12 hours with a single dose. Important added advantage: systemic clearance is almost complete after 24 hours.

ROCHE

LIPO GANTRISIN

simple as 1 2 3

antibacterial therapy with two doses daily

1 indications:

Systemic and urinary tract infections due to sulfa-susceptible microorganisms.

2 description:

With Lipo Gantrisin, therapeutic blood levels can usually be maintained for 12 hours with a single dose. Lipo Gantrisin contains Gantrisin Acetyl emulsified in a readily digestible vegetable oil for faster, higher and more prolonged blood levels. Each teaspoonful (5 cc) is equivalent to 1 Gm of sulfisoxazole (Gantrisin) in the form of acetyl sulfisoxazole.

3 properties:

Two doses a day of Lipo Gantrisin are usually adequate; however, two, four or six doses per 24 hours may be specified, as the physician thinks best. It offers these advantages: higher, more prolonged blood levels . . . wide antibacterial spectrum . . . no renal blocking . . . no need for alkalies . . . special convenience for children.

For dosage and supply refer to PDR p. 760

ROCHE®

ROCHE LABORATORIES

Division of Hoffmann-La Roche Inc • Nutley 10, New Jersey

LIPO GANTRISIN® ACETYL— BRAND OF ACETYL SULFISOXAZOLE

in iron deficiency anemia

the direct approach

...specific therapy

Fer-In-Sol®

iron in a drop for infants and children

"When iron is indicated give only iron. The therapeutic response will be infinitely better, the medication will be taken with greater facility, and the cost of treatment will be far less."*

In infants and children the most common anemia is that due to iron deficiency; peak incidence is seen in ages from 6 to 24 months.*

Specify Fer-In-Sol—well tolerated, efficiently utilized ferrous sulfate in an acidulous vehicle for better absorption. Its pleasant citrus flavor makes it readily acceptable to young children, and its dropper dosage form makes it easy to give.

You are cordially invited to ask your Mead Johnson Representative for the convenient Fer-In-Sol Dosage Card (Lit. No. 267) or write to us, Evansville 21, Indiana.

*Smith, N. J., and Rosello, S.: J. Clin. Nutrition *1*:275, (May-June) 1953.

Mead Johnson

Symbol of service in medicine

FE597

S-M-A expand

for the baby

S-M-A® FOOD FORMULA FOR INFANTS, WYETH

CONCENTRATED LIQUID • INSTANT POWDER

S-M-A protein is in physiologic proportion. The infant fed S-M-A receives a daily protein intake comparable to that of the breast-fed infant.

S-M-A fat is high in essential fatty acids. S-M-A supplies 20 calories per ounce, the same as human milk.

S-M-A provides *physiological* carbohydrate in the form of lactose in an amount (7%) closely adjusted to the average quantity in human milk.

S-M-A supplies vitamins and minerals in amounts adequate to meet the recognized needs of health and growth.

S-M-A for sound infant nutrition . . .

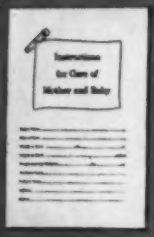
Wyeth

Philadelphia 1, Pa.

nd your baby-care resources

The S-M-A Service* (available only to physicians) includes vital information for expectant mothers. Not only does the service provide extensive infant-care information, but it also answers many questions about pre- and postnatal problems to supplement your instructions to the mother.

or the mother



A teaching aid on important points of care

Facts and pictures for the mother during pregnancy and her baby's first year of life

A personalized gift of S-M-A from you

or you, the physician

Rapid data for supplemental feeding

Authoritative discussions of nutritional requirements and infant-feeding problems

or the hospital

Baby-identification cards for the nursery

*Your Wyeth Territory Manager will gladly supply you, free of charge, with the *continuous* S-M-A Infant-Feeding Service for your obstetrical practice.

Choose the right iron

In medicine as in golf, the right iron assures best results!

For Simple Iron Deficiency Anemia—

MOL-IRON TABLETS **MOL-IRON LIQUID**

Each tablet or teaspoonful contains 195 mg. ferrous sulfate and 3 mg. molybdenum oxide. *Dosage for adults*—2 tablets or 2 teaspoonfuls liquid t.i.d. *For children*—1 tablet or ½ to 1 teaspoonful liquid t.i.d.

Supplied: Tablets—bottles of 100

Liquid—bottles of 12 fl. oz.

For Protection Against Iron Deficiency During Infancy

MOL-IRON DROPS

Especially well tolerated, highly palatable. Each cc. contains 125 mg. ferrous sulfate and 2 mg. molybdenum oxide. *Dosage for children up to 6 years*—0.3 cc. daily; *children more than 6*—0.6 cc. daily.

Supplied: Bottles of 15 cc. and 50 cc. with special dropper.

There is a

MOL-IRON® Tablet / Liquid / Drops

preparation for all orally treatable anemias

SUPERIOR TOLERANCE

"Of the 75 patients receiving iron [Mol-Iron] therapy, [only] one was forced to stop treatment...."[1]

OUTSTANDING EFFECTIVENESS

"We have never had other iron salts so efficacious...."[2]

RAPID RESPONSE

"...produced a substantially more rapid therapeutic response than ferrous sulfate, the difference...being statistically significant."[3]

ECONOMICAL THERAPY

Faster maximal hemoglobin response eliminates prolonged treatment.

Costs no more on prescription than ordinary iron salts!

References:

1. Lund, C. J.: Am. J. Obst. & Gynec. *62*:947, 1951. 2. Dieckmann, W. J., and Priddle, H. D.: Am. J. Obst. & Gynec. *57*:541, 1949. 3. Chesley, R. F., and Annitto, J. E.: Bull. Margaret Hague Mat. Hosp. *1*:68, 1948.

WHITE LABORATORIES, INC.
Kenilworth, New Jersey

an entirely new concept in broad-spectrum therapy

COSA

Cosa is an abbreviation for glucosamine, a basic substance older than man himself, found throughout the human body and in the whole spectrum of nature—lobster shells . . . mother's milk . . . eggs . . . gastric mucin. . . . It achieved new importance when Pfizer scientists discovered that this interesting compound provided the following significant advantages when added to antibiotics such as tetracycline and oxytetracycline:

what is COSA

1. Higher, faster antibiotic blood levels[1]
2. More consistent high antibiotic blood levels[2]
3. Effective, well-tolerated broad-spectrum therapy[3,4,5]
4. Safe, physiological potentiation with glucosamine, a nontoxic human metabolite[6,7,8]

References: **1.** Welch, H.; Wright, W. W., and Staffa, A. W.: Antibiotic Med. & Clin. Therapy *5*:52 (Jan.) 1958. **2.** Carlozzi, M.: Ibid. *5*:146 (Feb.) 1958. **3.** Shalowitz, M.: Clin. Rev. *1*:25 (April) 1958. **4.** Stone, M. L.; Bamford, J., and Bradley, W.: Antibiotic Med. & Clin. Therapy *5*:322 (May) 1958. **5.** Cornbleet, T.; Chesrow, E., and Barsky, S.: Ibid. *5*:328 (May) 1958. **6.** West, R., and Clarke, D. H.: J. Clin. Invest. *17*:173 (March) 1938. **7.** Jimenez-Diaz, C.; Aguirre, M., and Arjona, E.: Bull. Inst. M. Res. Madrid *6*:137 (Oct.-Dec.) 1953. **8.** Lerman, S.; Pogell, B. M., and Lieb, W.: A.M.A. Arch. Ophth. *57*:354 (March) 1957.

Your patients will do better when you choose COSA antibiotics

COSA-TETRACYN*

GLUCOSAMINE-POTENTIATED TETRACYCLINE

This excellently tolerated formulation provides highest, fastest blood levels of tetracycline, the most widely used broad-spectrum antibiotic. Capsules (black and white) 250 mg. and 125 mg.; orange-flavored Oral Suspension, 125 mg. per 5 cc.

COSA-SIGNEMYCIN*

TRIACETYLOLEANDOMYCIN GLUCOSAMINE-POTENTIATED TETRACYCLINE

Provides broad-spectrum antibiotic activity (Cosa-Tetracyn) *plus* triacetyloleandomycin effectiveness against many organisms resistant to currently used antibiotics. Recommended for home or office where sensitivity testing is difficult or impractical. Capsules (green and white) 250 mg. and 125 mg.

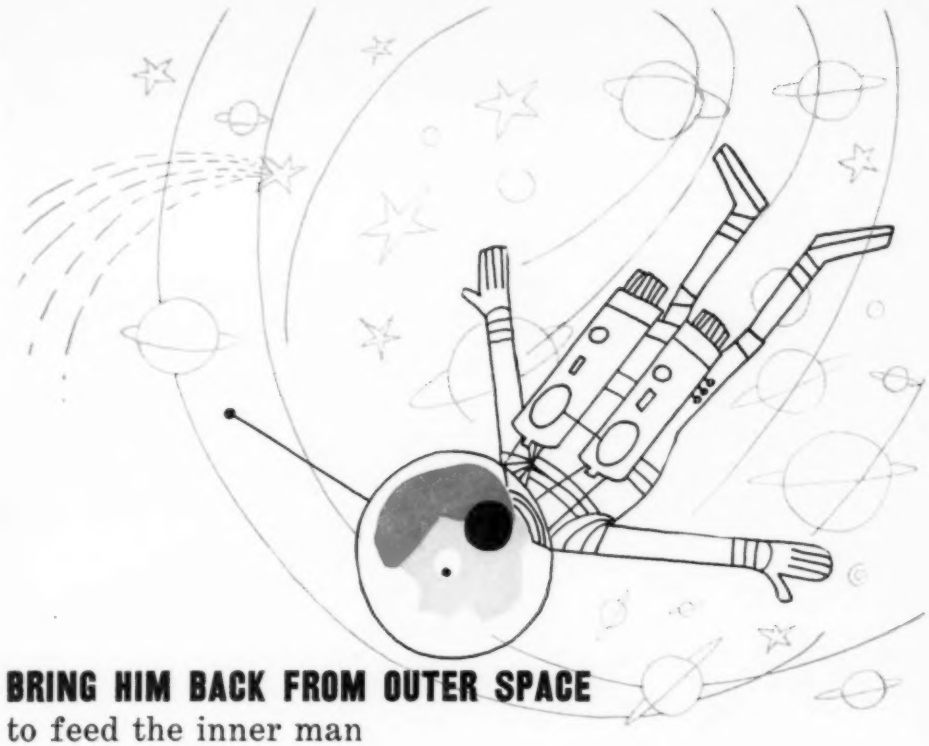
COSA-TERRAMYCIN*

OXYTETRACYCLINE WITH GLUCOSAMINE

A proven standard in antibiotic therapy for over 8 years now significantly improved through (1) glucosamine potentiation, (2) additional recrystallizations for maximum purity. Capsules (yellow) 250 mg. and 125 mg.; peach-flavored Oral Suspension, 125 mg. per 5 cc.

Researching the future—today

Pfizer PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y. *Trademark



BRING HIM BACK FROM OUTER SPACE
to feed the inner man

REDISOL®

CYANOCOBALAMIN (CRYSTALLINE VITAMIN B_{12})

Anorectic space cadets zoom in for meals when REDISOL takes hold. This dietary supplement—Vitamin B_{12}—often stimulates appetite with consequent weight gain.

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1. Cornely, D. A., and Ritter, J. A.: N-acetyl-p-aminophenol (Tylenol Elixir) as a Pediatric Antipyretic-Analgesic, J.A.M.A. *160*:1219 (Apr. 7) 1956.

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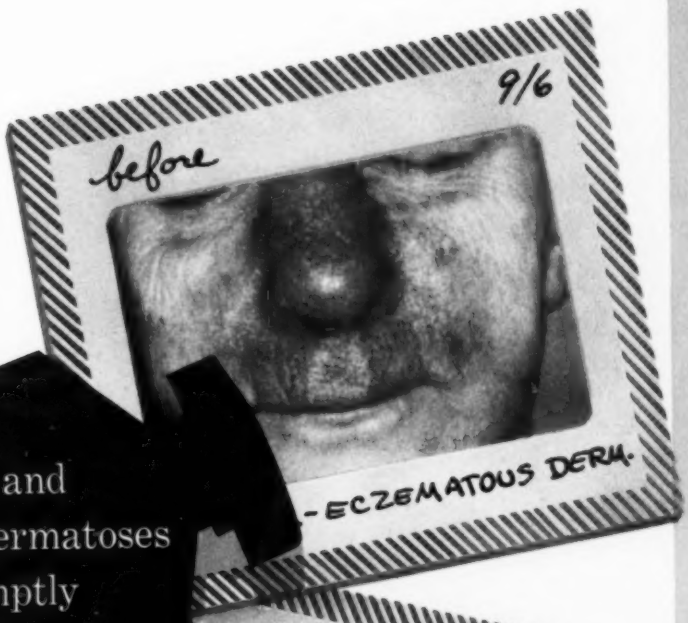

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BIBLIOGRAPHY: (1) Hagedorn, A. B.: J.A.M.A. *164*:1642 (Aug. 10) 1957. (2) Brown, E. B., and Moore, C. V., in Tocantins, L. M.: Progress in Hematology, New York, Grune & Stratton, Inc., 1956, vol. 1, p. 25. (3) Hagedorn, A. B.: M. Clin. North America, Philadelphia, W. B. Saunders Company (July) 1956, p. 983. (4) Grunberg, A., and Blair, J. L.: A.M.A. Arch. Int. Med. *96*:731, 1955. (5) Baird, I. M., and Podmore, D. A.: Lancet *2*:942 (Nov. 6) 1954. (6) Cappell, D. F.; Hutchison, H. E.; Hendry, E. B., and Conway, H.: Brit. M. J. *2*:1255 (Nov. 27) 1954. (7) Millard, J. B., and Barber, H. S.: Ann. Rheumat. Dis. *15*:51, 1956. (8) Cope, E.; Gillhespy, R. O., and Richardson, R. W.: Brit. M. J. *2*:639 (Sept. 15) 1956. (9) Jennison, R. F., and Ellis, H. R.: Lancet *2*:1245 (Dec. 18) 1954. (10) Scott, J. M., and Govan, A. D. T.: Brit. M. J. *2*:1257 (Nov. 27) 1954. (11) Scott, J. M.: Brit. M. J. *2*:635 (Sept. 15) 1956. (12) Gaisford, W., and Jennison, R. F.: Brit. M. J. *2*:700 (Sept. 17) 1955. (13) Wallerstein, R. O., and Hoag, M. S.: Scientific Exhibit, Sixth Internat. Cong., Internat. Soc. Hemat., Boston, Mass., Aug. 27-Sept. 1, 1956. (14) Wallerstein, R. O.: J. Pediat. *49*:173, 1956. (15) Sturgeon, P.: Pediatrics *18*:267, 1956. (16) Wallerstein, R. O., and Hoag, M. S.: J.A.M.A. *164*:962 (June 29) 1957.

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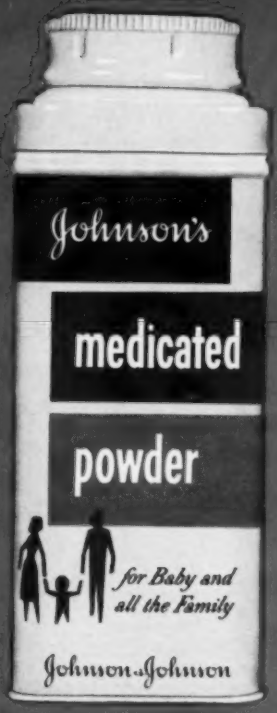

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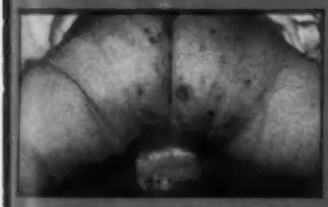

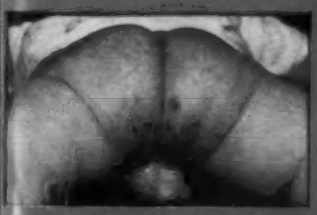

Top: Patient R. R.—Severe "diaper rash" with secondary infection at start of treatment, 12/26/56.

Bottom: Eight days after treatment with JOHNSON'S MEDICATED POWDER, 1/3/57. Almost complete clearing of initial rash and of secondary infection.

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References: 1. Council on Drugs, A.M.A.: J.A.M.A. 166:52, 1958. 2. Pulaski, E. J.: Practitioner 179:463, 1957. 3. Cronk, G. A., and Naumann, D. E.: Ant. Med. & Clin. Ther. 4:166, 1957. 4. Kaplan, M. A., Dickison, H. L., Hubel, K. A., and Buckwalter, F. H.: Ibid. 4:99, 1957. 5. Prigot, A., Shidlovsky, B. A., and Felix, A. J.: Ibid. 4:287, 1957. 6. Pulaski, E. J., and Isokane, R. K.: Ibid. 4:408, 1957. 7. Putnam, L. E.: Ibid. 4:470, 1957. 8. Rein, C. R., and Fleischmajer, R.: Ibid. 4:421, 1957. 9. Welch, H., Lewis, C. N., Stalfa, A. W., and Wright, W. W.: Ibid. 4:215, 1957. 10. Cronk, G. A., Naumann, D. E., and Casson, K.: Antibiotics Annual, 1957-8, ed. by H. Welch and F. Marti-Ibanez, Medical Encyclopedia, New York, p. 397. 11. Dube, A. H.: Ibid. p. 409. 12. Hubel, K. A., Palmeri, B., and Isunn, P. A.: Ibid. p. 443. 13. Kaplan, M. A., Albright, H., and Buckwalter, F. H.: Ibid. p. 415. 14. Portnoy, B., Draper, T., and Wehrle, P. F.: Ibid. p. 386. 15. Shidlovsky, B. A., Prigot, A., Maynard, A. de L., Felix, A. J., and Hjelt-Harvey, I.: Ibid. p. 459. 16. Cronk, G. A.: Personal communication.

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(1) Hansen, A. E., et al.: Fed. Proc. 16: 387, 1957;
(2) Hansen, A. E.: Pediat. 21: 494, 1958.

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References: **Carlozzi, M.:** Antibiotic Med. & Clin. Therapy *5*:146 (Feb.) 1958. **Shalowitz, M.:** Clin. Rev. *1*:30 (April) 1958.

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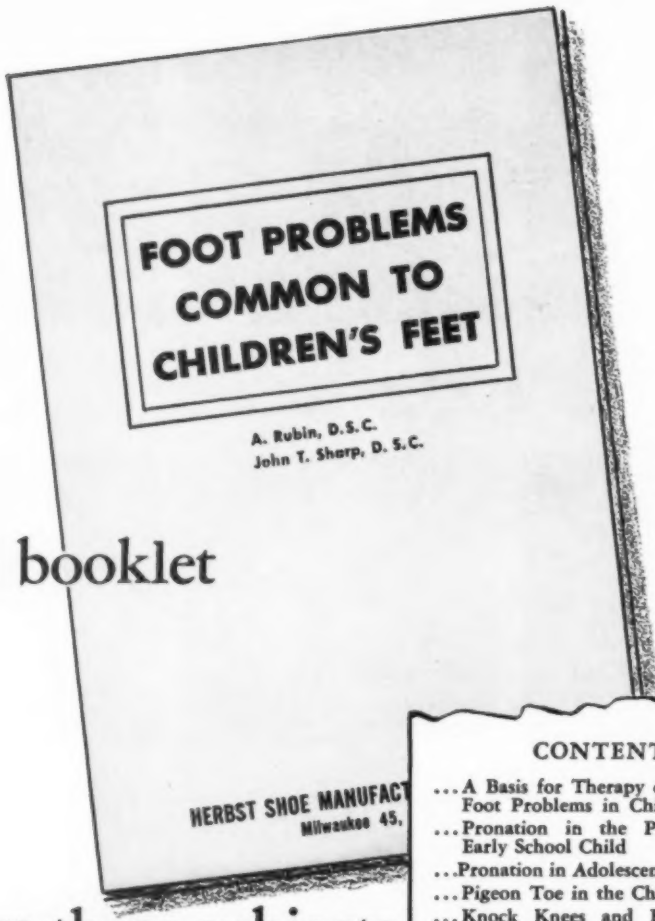

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* Fries, J. H., Milk Allergy-Diagnostic Aspects and the Role of Milk Substitutes, J.A.M.A., Nov. 23, 1957.

** Ibid.

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References: 1. Rittenhouse, E. A.: Prevention of Secondary Hemorrhage in Tonsillectomy, E.E.N.T. Mo. 36:406 (July) 1957. 2. Fox, S. L.: Tonsillectomy and Adenoidectomy in Review, Clin. Med. 4:699 (June) 1957. 3. Granberry, C., and Beatrous, W. P.: Effect of a New Chewing Troche on Post-Tonsillectomy Morbidity, E.E.N.T. Mo. 36:294 (May) 1957.

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1. Lewis, J.M., et al.: J. Pediat. 31:496.

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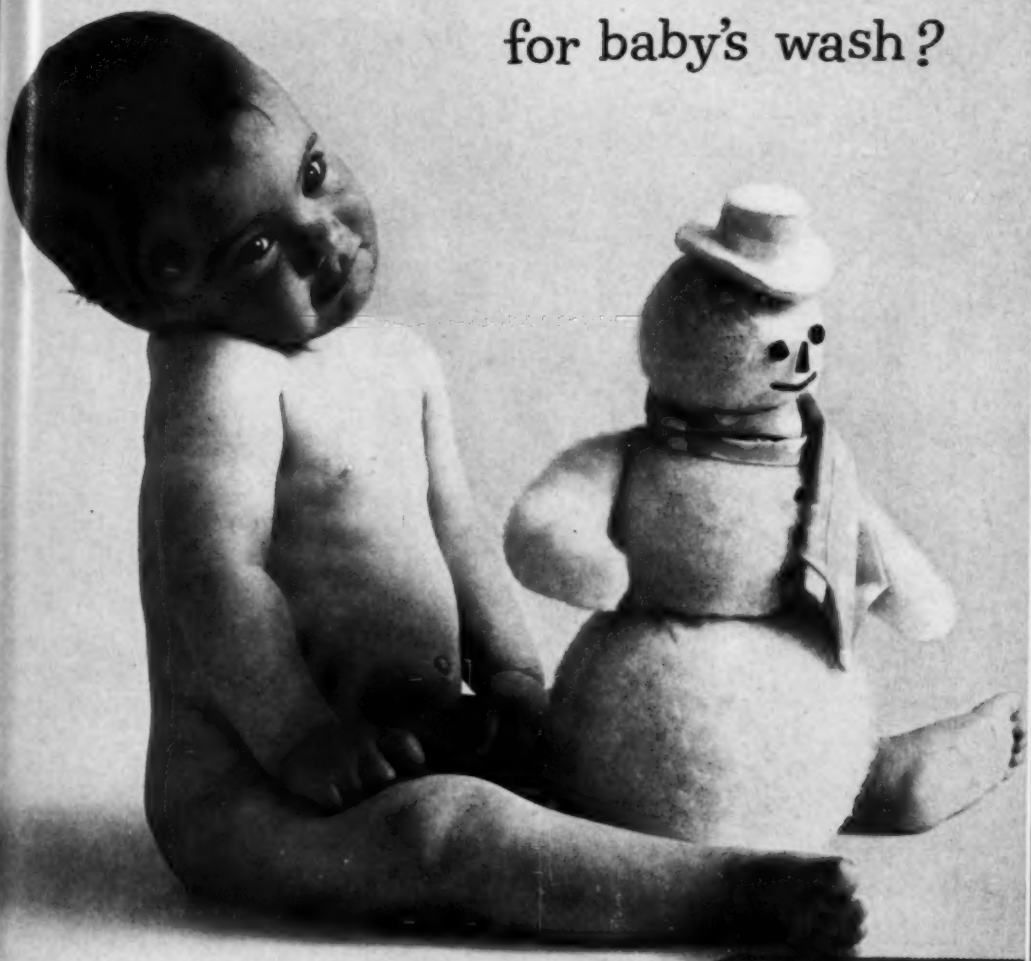

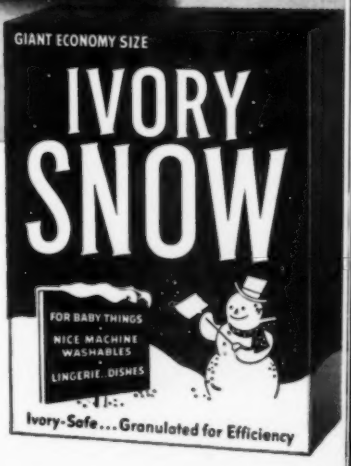

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1. Koessler, H. W.: Arch. Ped. 74:47 (Feb.) 1957.
2. Kahan, H. *et al.*: Arch. Ped. 73:125 (Apr.) 1956.
3. Editorial: J.A.M.A. 165:254 (Sept. 21) 1957.

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Multiple spoonful doses are best measured into a glass and taken at one time—without dilution. Although rarely required, dosage may be repeated if necessary after 6 or 8 hours. Other theophylline or ephedrine preparations should not be administered with Elixophyllin.

PEDIATRIC DOSAGE TABLE

Age	Dose	Approx. Household Measure
6 months	2.4 cc.	½ teaspoonful
1 year	4.6 cc.	1 teaspoonful
2½ years	10 cc.	2 teaspoonfuls
4 years	15 cc.	1 tablespoonful
60 lbs.	22.5 cc.	1½ tablespoonfuls
80 lbs.	30 cc.	2 tablespoonfuls
100 lbs.	37.5 cc.	2½ tablespoonfuls
120 lbs.	45 cc.	3 tablespoonfuls

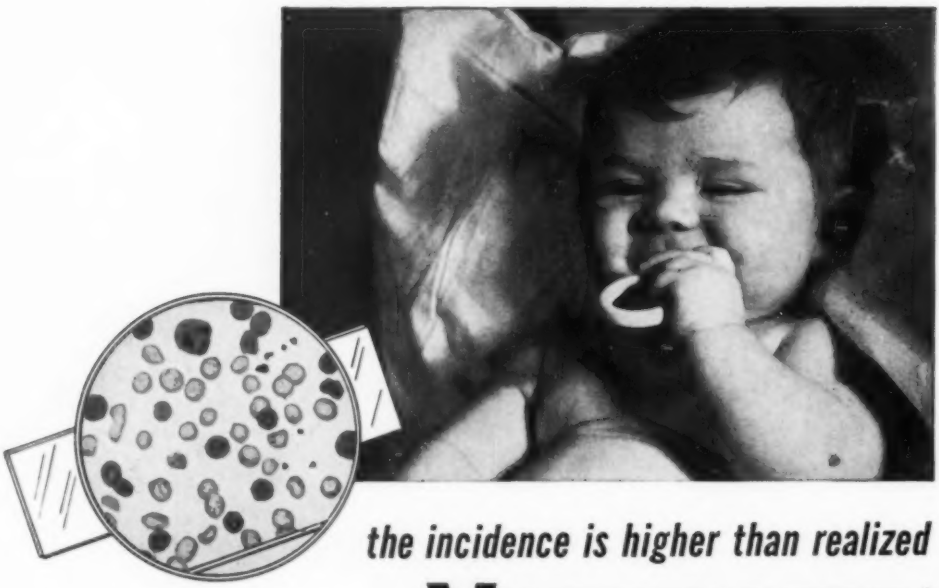
oral ELIXOPHYLLIN

Sherman Laboratories

**A folio of all published studies on request*

Detroit 11, Michigan

Heavy Metal Poisoning



the incidence is higher than realized

Calcium Disodium **VERSENATE***

spells the answer

At last, here is a dependably effective means of removing heavy metals from the body *without danger of organ damage.* Calcium Disodium VERSENATE is now available for oral as well as intravenous therapy; the intravenous form for safe, effective, dramatic short-term treatment; the oral form for convenient prevention of exacerbations or as sole therapy for milder types of lead poisoning.

NOW IN 2 DOSAGE FORMS

Write for descriptive booklet

INTRAVENOUS Complete instructions for dilution and administration accompany the ampuls. The average daily dose for children is not more than 0.5 Gm. per 35 pounds of body weight, given once or twice daily. (Adult dose, 1 to 2 Gm. per day, given as two infusions.) In boxes of six 5 cc. (1 Gm.) ampuls.

ORAL For children, the dose is adjusted on the basis of 2 tablets (1 Gm.) per 35 pounds of body weight daily, in divided doses. For ease of administration tablets may be crushed and dissolved in milk. (Average adult dose is 8 tablets (4 Gm.) per day, in divided doses.) In bottles of 250 tablets, each containing 500 mg.

*Trademark of Dow Chemical Co.

Riker LOS ANGELES

VIFORT®

(Aqueous Polyvitamin)

DROPS

- completely water-soluble... including vitamins A and D
- 3 to 5 times better absorbed, utilized, and stored than from oily media
- deliciously orange-flavored... a treat for infants and growing children
- backed by years of clinical study and pediatric application

Dosage: 0.3 to 0.6 cc. daily; may be placed directly on tongue or taken in fruit juices or milk.

Supplied: bottles of 15, 30, and 60 cc. with graduated dropper.

Also available: VIFORT Capsules, bottles of 30 and 100.

Samples? Literature? Write–

ENDO LABORATORIES INC. Richmond Hill 18, New York

Endo®

LOOK MA!

NO MORE DIAPER RASH that **ACID MANTLE®** IS SURE SWELL!

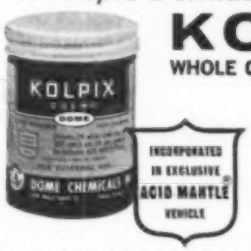
Baby's sensitive skin is best protected by the use of **ACID MANTLE - CREME or LOTION — pH 4.2.** It instantly restores normal acidity to the skin which has been made alkaline, due to contact with urine. It thus prevents diaper rash.

AVAILABLE: Creme in 4 oz. plastic jar, Lotion in 4 oz. plastic squeeze bottle.

For Atopic Dermatitis in Infants and Children:

KOLPIX® CREME

WHOLE CRUDE COAL TAR in the exclusive ACID MANTLE base

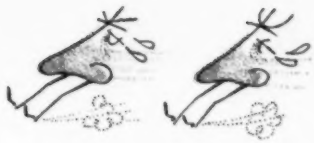


Light gray, non-greasy, non-staining water washable creme base. "We believe tars to be the best local remedy for atopic dermatitis in infants and children." — Urbach, F., and Jacobson, C.: In Pediatric Dermatology, Pediatric Clinics of North America, Philadelphia & London, W. B. Saunders Co., August 1956, p. 619.

DOME *Chemicals Inc.*

NEW YORK 23 • LOS ANGELES 46 • *In Canada:* 2765 Bates Rd., Montreal, P.Q.

running noses . . .



caused by pollen allergies

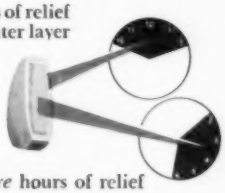
TRIAMINIC stops rhinorrhea, congestion and other distressing symptoms of summer allergies, including hay fever. Running nose, watery eyes and sneezing are best relieved by antihistamine *plus* decongestant action – systemically – with TRIAMINIC.

This new approach frequently succeeds where less complete therapy has failed. It is not enough merely to use histamine antagonists; ideally, therapy must be aimed also at the congestion of the nasal mucosa. Triaminic provides such effective combined therapy in a single timed-release tablet.

TRIAMINIC brings relief in minutes–lasts for hours. Running noses stop, congested noses open–and stay open for 6 to 8 hours.

Triaminic provides around-the-clock freedom from allergic congestion with just one tablet t.i.d. because of the special timed-release design.

first–3 to 4 hours of relief from the outer layer



then–3 to 4 *more* hours of relief from the inner core

Dosage: One tablet in the morning, mid-afternoon and at bedtime. In postnasal drip, one tablet at bedtime is usually sufficient.

Each timed-release TRIAMINIC Tablet contains:

Phenylpropanolamine HCl	50 mg.
Pheniramine maleate	25 mg.
Pyrilamine maleate	25 mg.

TRIAMINIC FOR THE PEDIATRIC PATIENT

TRIAMINIC Juvelets*, providing easy-to-swallow half-dosages for the 6- to 12-year-old child, with the timed-release construction for prolonged relief.

*Trademark

TRIAMINIC Syrup, for those children and adults who prefer a liquid medication. Each 5 ml. teaspoonful is equivalent to ¼ Triaminic Tablet or ½ Triaminic Juvelet.

Triaminic®

SMITH-DORSEY • a division of The Wander Company • Lincoln, Nebraska • Peterborough, Canada

ELIOT

Inhalation Therapy Equipment for *Children*

CROUP TENT: Designed especially for Children to provide oxygen and aerosol therapy with effective ice cooling. Made of durable 20-gage vinyl, its small cubical volume achieves 90 percent R.H. at 70° F and less than 1 percent CO_2 at 8 to 12 lpm oxygen flow. The swinging, drip-proof ice tray permits its use with the patient in lying or sitting position, and the zippered slit above the ice tray permits easy filling with minimum oxygen loss. An attached pouch holds an ELIOT Neb (EL) izer.

AEROSOL and OXYGEN MASK: Sturdy, well-designed face tent ideally suited for oxygen or aerosol therapy either separately or simultaneously administered in individually controlled amounts. This is a light weight tent providing 100% visibility with adjustable plastic head bands insuring maximum comfort.

Through the years, ELIOT "Clinically Proven Products" has come to mean high quality oxygen therapy equipment. Now these fine products are available exclusively through any of the 59 Medical Sales and Service Offices of NCG . . . an office or branch in every principal city. Contact the one nearest you today.

NCG®

NATIONAL CYLINDER GAS
Division of CHEMETRON CORPORATION
840 N. MICHIGAN AVE. • CHICAGO 11, ILL.

CHEMETRON

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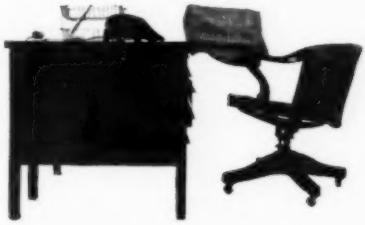
when you treat common bacterial infections...



a well patient back on the job

measures therapeutic success

Pentids

Squibb 200,000 Unit Buffered Penicillin G Potassium Tablets

when an oral penicillin is indicated...prescribe Pentids

Six years experience by physicians in treating many millions of patients with Pentids confirm clinical effectiveness and safety. Excellent results are obtained with Pentids in many common bacterial infections with only 1 or 2 tablets t.i.d. Pentids may be taken without regard to meals. Pentids are economical... cost less than other penicillin salts.

DOSE: 1 or 2 tablets t.i.d. without regard to meals

SUPPLY: Bottles of 12, 100 and 500 tablets

other **Pentids** *products*

NEW Pentids For Syrup: Squibb Flavored Penicillin Powder: when prepared with 35 cc. of water, the preparation provides 60 cc. of fruit-flavored syrup, 200,000 units per teaspoonful (5 cc.).

Pentids Capsules: Squibb Penicillin G Potassium 200,000 Unit Capsules, bottles of 24, 100 and 500.

Pentids Soluble Tablets: Squibb Penicillin G Potassium Soluble Tablets—200,000 units, vials of 12, bottles of 100.

Pentid-Sulfas Tablets: Squibb Penicillin with Triple Sulfas, bottles of 30, 100 and 500.

These formulations are given ½ hr. before meals or 2 hrs. after meals.

SQUIBB *Squibb Quality—the Priceless Ingredient*

"PENTIDS"® IS A SQUIBB TRADEMARK

when nausea and vomiting bring a plea for help . . .

suggest first aid with . . .

EMETROL®

PHOSPHORATED CARBOHYDRATE SOLUTION

a safe, pleasant-tasting, oral antiemetic . . .

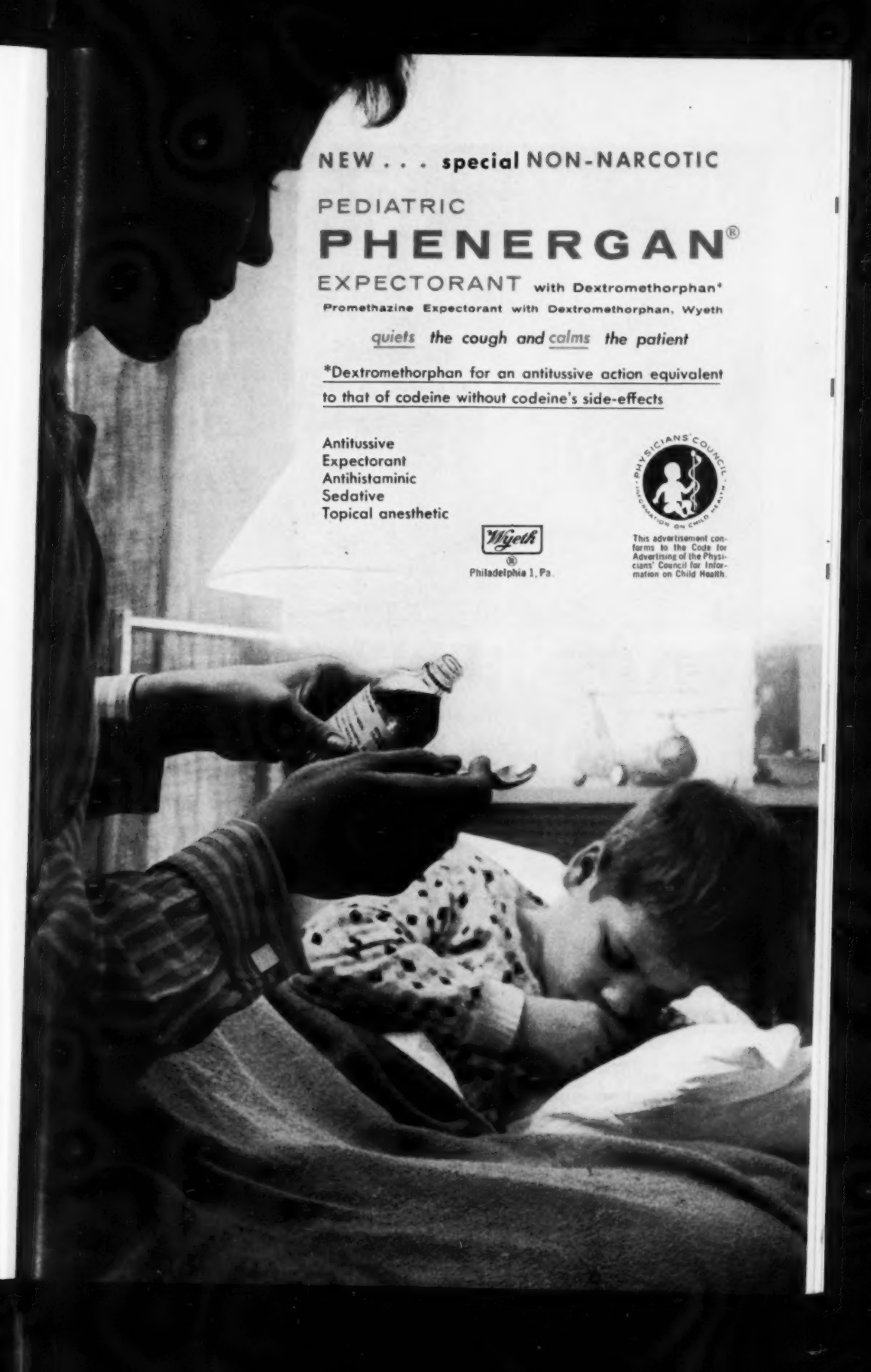
effective in 6 out of 7 cases of functional vomiting[1]—often associated with intestinal "flu" or G.I. grippe. Rapidly effective . . . economical . . . and *safe physiologic action* usually eliminates need for potentially hazardous antiemetic drugs. Also established for safe relief of "morning sickness."[2]

Dose: children, 1 or 2 tsp.; adults, 1 or 2 tbsp.; repeat every 15 minutes until vomiting ceases. In bottles of 3 and 16 fl.oz. DO NOT DILUTE.

1. Bradley, J. E., et al.: J. Pediat. 38:41, 1951. 2. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. 65:311, 1953.

Kinney®

KINNEY & COMPANY, INC. COLUMBUS, INDIANA


NEW . . . special NON-NARCOTIC
PEDIATRIC
PHENERGAN®
EXPECTORANT with Dextromethorphan*
Promethazine Expectorant with Dextromethorphan, Wyeth
quiets the cough and calms the patient
*Dextromethorphan for an antitussive action equivalent to that of codeine without codeine's side-effects
Antitussive
Expectorant
Antihistaminic
Sedative
Topical anesthetic
Wyeth
Philadelphia 1, Pa.
PHYSICIANS' COUNCIL INFORMATION ON CHILD HEALTH
This advertisement conforms to the Code for Advertising of the Physicians' Council for Information on Child Health.

IN TREATMENT OF PINWORMS

break the reinfestation cycle rectally

GENTIAN-EV SUPPRETTES®

SUCCESSOR / TO THE SUPPOSITORY

97% CURES

Within 14-28 days, virtually a 100% cure of pinworms can be obtained with combined oral medication and Gentian-Ev Supprettes rectally.[1]

NEW
TWO-PHASE ATTACK

RECTALLY—Gentian-Ev Supprettes

- Break reinfestation cycle
- Kill gravid females in rectal region
- Arrest perianal itching, scratching

ORALLY—Oxyuricidal Medication

- Destroys young and adult oxyuricides in intestinal tract

THE "NEOCERA" BASE

Contains no oils or fatty materials. Consists of water-soluble Carbowaxes* with active dispersal agent.

*Trademark U.C.C.

1. Allen, F. P., Jr.: J. Ped. 46: 155, 1955.

Composition: Each Gentian-Ev Supprette contains gentian violet 0.25% and benzocaine 2.0%, in "Neocera" dispersal base.

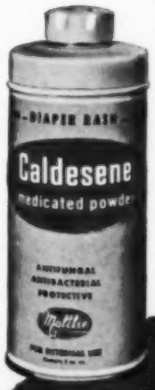
Supplied: In jars of 14 (one complete treatment).

NO REFRIGERATION NECESSARY
Samples on Request

GENTIAN-EV SUPPRETTES

RECTAL MANAGEMENT OF ENTEROBIUS VERMICULARIS

Webster **THE WILLIAM A. WEBSTER COMPANY, MEMPHIS 5, TENNESSEE**



prevention • treatment

Caldesene®
medicated powder

The medication makes the big difference: Caldesene contains 15% calcium undecylenate for sustained antibacterial and antifungal action – Caldesene forms a protective coating which prevents moisture or other irritants from coming into contact with tender or affected areas. Since the film is discontinuous it does not interfere with insensible perspiration. This unique product relieves itching, soreness and burning, and protects against diaper rash, prickly heat, and chafing.

Supplied in 2 oz. shaker containers.

FOR A TRIAL SUPPLY WRITE TO
PROFESSIONAL SERVICE DEPARTMENT

Maltbie

MALTBIE LABORATORIES DIVISION
WALLACE & TIERNAN INC.

Belleville 9, New Jersey

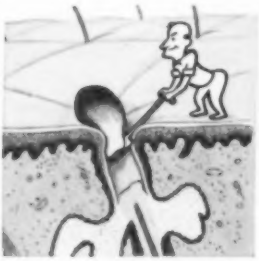
PCD-71

IN ACNE

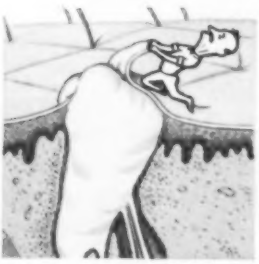
Fostex® degreases the skin and helps remove blackheads

Fostex contains a combination of surface active agents (Sebulytic*) which:

◂ Completely emulsify excess oil so that it is quickly washed off the skin.



◂ Penetrate and soften comedones, unblocking the pores and facilitating removal of sebum plugs.



Fostex dries and peels the skin

◂ The Sebulytic base of Fostex dries and promotes peeling of the skin . . . actions enhanced by the keratolytic effects of micropulverized sulfur and salicylic acid.

*(Sodium lauryl sulfoacetate, sodium alkyl aryl polyether sulfonate, sodium dioctyl sulfosuccinate.)

Fostex is easy for your patients to use

FOSTEX CREAM
for therapeutic washing of skin in the initial phase of acne treatment, when maximum degreasing and peeling are desired.

FOSTEX CAKE
for maintenance therapy to keep skin dry and substantially free of comedones.

◂ Patients stop using soap on affected skin areas. Instead they use Fostex for therapeutic washing of the skin. The Fostex lather is massaged into the skin for 5 minutes—then rinse and dry.

Write for samples

WESTWOOD *Pharmaceuticals*
Division of Foster-Milburn Co.
468 Dewitt Street • Buffalo 13, New York

from "no helpings" to "second helpings"

TROPH-IRON*

B_{12}—Iron—B_1

The high potency formula of 'Troph-Iron' Liquid and 'Troph-Iron' Tablets is designed to stimulate appetite, promote growth and correct nutritional iron deficiency. And the usual dosage is only one teaspoonful or tablet a day.

Each teaspoonful (5 cc.) or tablet of 'Troph-Iron' supplies:

Vitamin B_{12}	25 mcg.
Vitamin B_1	10 mg.
Ferric pyrophosphate . .	250 mg.

The liquid preparation has a delicious cherry flavor that insures cooperation when it's time for 'Troph-Iron'.

Smith Kline & French Laboratories, Phila

*T.M. Reg. U.S. Pat. Off.

For bacterial diarrheas—new effectiveness . . .

1. Powerful new adsorbent . . .
five times as adsorbent as kaolin

Proof of adsorptive superiority

1 Gm. CLAYSORB plus dye

Dye is completely adsorbed.

1 Gm. KAOLIN
plus same amount of dye

Much of the dye is still unadsorbed.

5 Gm. KAOLIN
plus same amount of dye

Five times as much kaolin is necessary to adsorb the dye.

Supplied: Bottles of 8 fl. oz.

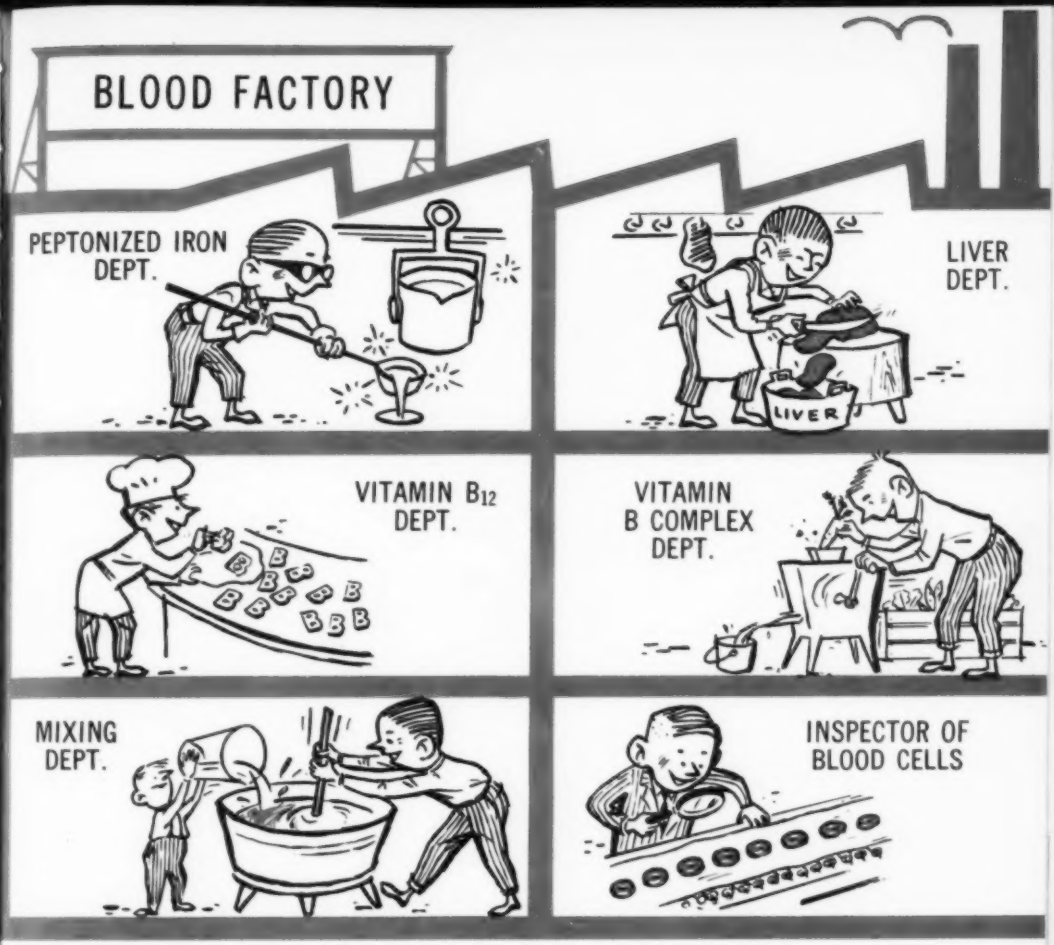
Polymagma®

Wyeth
Philadelphia 1, Pa.

Dihydrostreptomycin Sulfate, Polymyxin B Sulfate, and Pectin with Claysorb* (Activated Attapulgite, Wyeth) in Alumina Gel, Wyeth

*Trademark

- POWERFUL NEW ADSORBENT
- SYNERGISTIC ANTIBIOTICS
- LOW DOSE
- PLEASANT TASTE
- WELL-TOLERATED



The preferred hematinic with **PEPTONIZED** *iron*

LIVITAMIN®

Peptonized iron is virtually predigested. It is absorbed as well as ferrous sulfate, and is one-tenth as irritating to the gastric mucosa. Anemias refractory to other forms of iron will often respond promptly to Livitamin therapy.

The Livitamin formula, containing the B complex, provides integrated therapy to correct the blood picture, and to improve appetite and digestion.

Each fluidounce contains:

Iron peptonized	420 mg.
(Equiv. in elemental iron to	71 mg.)
Manganese citrate, soluble	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Vitamin B_{12} Activity (derived from Cobalamin conc.)	20 mcg.
Nicotinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

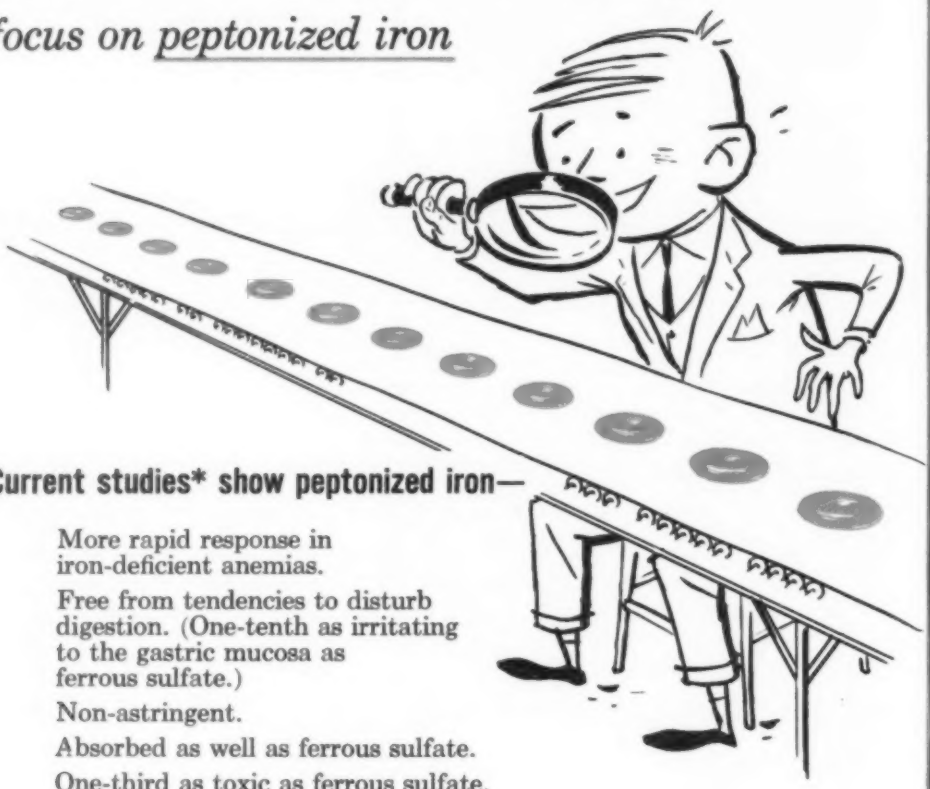
The S. E. MASSENGILL Company

BRISTOL, TENNESSEE

NEW YORK • KANSAS CITY • SAN FRANCISCO

For predictable therapeutic advantages . . .

focus on peptonized iron



Current studies* show peptonized iron—

More rapid response in iron-deficient anemias.

Free from tendencies to disturb digestion. (One-tenth as irritating to the gastric mucosa as ferrous sulfate.)

Non-astringent.

Absorbed as well as ferrous sulfate.

One-third as toxic as ferrous sulfate.

LIVITAMIN® with Peptonized Iron

Currently, mailings will be forwarded only at your request. Write for samples and literature.

*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition *1*:35 (Jan.-Feb., 1957).

The S. E. MASSENGILL Company

BRISTOL, TENNESSEE

NEW YORK • KANSAS CITY • SAN FRANCISCO

Higher and higher...
till the sky tipped over...
then down she came into the brambles
and sharp gravel and her dress was torn and there
were cuts and scratches...along with smudges of dirt

moral of the story: falling from a swing is bad even for a rag doll . . .
and when real children are hurt at play, topical infections often follow.

to prevent and control topical infections

prescribe **NEO-POLYCIN™**

...because it provides the 3 preferred topical antibiotics

Neomycin
Polymyxin
Bacitracin

PITMAN-MOORE COMPANY
DIVISION OF ALLIED LABORATORIES, INC., INDIANAPOLIS 6, INDIANA

In the unique Fuzene® base which releases greater antibiotic concentrations than do ordinary grease-base ointments.

Supplied in 15 Gm. tubes.

temper tantrums tics, stuttering asthma hyperkinesia nightmares enuresis

These common pediatric problems[1-4] all respond to ATARAX Syrup[1-5] (and it's the "safest of the mild tranquilizers"[5])

Dosage: **Since many physicians report good results when the recommended dosage was doubled or tripled, the physician should be guided by patient response. Children (3 to 6 years), usually one teaspoon syrup or one 10 mg. tablet three times daily; (over 6 years), usually two teaspoons syrup or two 10 mg. tablets three times daily. Adults, usually one tablespoon syrup or one 25 mg. tablet four times daily.**

Supplied: **Tablets, tiny 10 mg. (orange), 25 mg. (green) and 100 mg. (red), bottles of 100. Syrup, 10 mg. per tsp. pint bottles. Prescription only.**

References: **1. Nathan, L. A. and Andelman, M. B.: Illinois M. J. 112:171 (Oct.) 1957. 2. Ayd, F. J. Jr.: New York State J. Med. 57:1742 (May 15) 1957. 3. Bayart, J.: presented at International Congress of Pediatrics, Copenhagen, Denmark, July 22-27, 1956. 4. Ayd, F. J. Jr.: Calif. Med. 87:75 (Aug.) 1957. 5. Ayd, F. J. Jr.: presented at Ohio Academy of General Practice, 7th Annual Scientific Assembly, Sept. 18-19, 1957.**

in children, too...

PEACE OF MIND ATARAX® (BRAND OF HYDROXYZINE) Tablets-Syrup

Rx PFIZER

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.

White's

DELECTAVITES

A complete one a day "vita-mineral" supplement in delectable, chocolate-like, foil wrapped nuggets— to satisfy a natural desire and to fill a physiologic need —**PLEASANTLY**

Each delicious foil wrapped nugget contains:

Vitamin A	5,000 U.S.P. Units	Biotin	30 mcg.
Vitamin D	1,000 U.S.P. Units	Rutin	12 mg.
Vitamin C	75 mg.	Calcium	50 mg.
Vitamin E	2 Int. Units	Boron	0.1 mg.
Vitamin B_1	2.5 mg.	Cobalt	0.1 mg.
Vitamin B_2	2.5 mg.	Fluorine	0.1 mg.
Vitamin B_6	1 mg.	Iodine	0.2 mg.
Vitamin B_{12} Activity	3 mcg.	Magnesium	3.0 mg.
Panthenol	5 mg.	Manganese	1.0 mg.
Nicotinamide	20 mg.	Molybdenum	1.0 mg.
Folic Acid	0.1 mg.	Potassium	2.5 mg.

DOSE: **ONE DELECTAVITE NUGGET DAILY** • SUPPLY: Box of 30 (one month's supply) • Box of 90 (three months' supply)

ONLY DELECTAVITES CAN BE CHEWED WITHOUT EVEN A TRACE OF VITAMIN FLAVOR!

WHITE LABORATORIES, INC., Kenilworth, N. J.

Swift meats play an essential role in a baby's "Pyramid of Growth"

New findings at the University of Rochester suggest that meat is a protective food, too. That when fed to premature infants it markedly decreases the tendency toward iron deficiency anemia during the first year of life. Also that its nutritional values are utilized at a far earlier age than has been supposed. This adds a third leg to what we at Swift have termed the "Pyramid of Growth". For the truly wonderful power of meat to build bodies, and its taste satisfactions, have for years been known and widely accepted. Protection . . . another excellent reason why *Delicious Meats are Swift's Specialty . . . especially Swift's Meats for Babies.*

Swift
103RD YEAR

New

liquid pediatric analgesic-antipyretic

Liquiprin*

for children

safer than aspirin, easier to use

for infants' and children's fever, discomfort of colds, minor aches and pains and following immunizations.

LIQUIPRIN is a suspension of salicylamide—chemically and pharmacologically distinctive from aspirin and other salicylates. Clinically, its analgesic-antipyretic action is approximately the same as that of aspirin, but its therapeutic action does not depend on conversion to salicylate, salicylic acid or their metabolites.

LIQUIPRIN offers these major advantages:

1. safer than aspirin
2. less gastric irritation
3. helps calm the feverish, fretful child
4. easier on the child with gastrointestinal upset
5. more rapidly absorbed
6. relieves minor aches and pains—reduces fever

administration: Convenient liquid form, pleasant taste and calibrated dropper make for easy accurate administration...directly from dropper or mixed with fruit juice, formula or milk. Each ½ dropper contains 1¼ gr. of salicylamide.

dosage: ½ dropper for each year of age, not to exceed 2 droppers (5 gr.).

◀ **added safety:** LIQUIPRIN is supplied in non-spill safety bottles. LIQUIPRIN is safer than aspirin—and made safer still because children cannot pour or drink the medication from this new, **exclusive** safety container.

available: bottles of 50 cc., 1 gr. salicylamide per cc.

bettering baby care through specialized research

*TRADEMARK FOR SALICYLAMIDE SUSPENSION, JOHNSON & JOHNSON.

Johnson & Johnson

anti-diaper rash

because

it is

anti-irritant

DESITIN®
OINTMENT

DESITIN OINTMENT is effectively impervious to urine, excrement, perspiration and secretions — and so it is effectively *anti-irritant*. One soothing, protective, healing application acts for hours in helping to prevent and clear up . . .

DIAPER RASH
irritation, chafing
excoriation

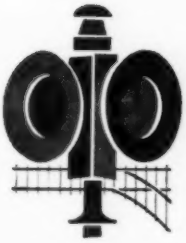
DESITIN OINTMENT—rich in cod liver oil (with its unsaturated fatty acids and natural vitamins A and D)—is the most widely used ethical specialty for the over-all care of the infant's skin.

Tubes of 1 oz., 2 oz., 4 oz., and 1 lb. jars

May we send SAMPLES and literature?

DESITIN CHEMICAL COMPANY
812 Branch Ave., Providence 4, R. I.

announcing...oral iron under
chelate control for a
SURER HEMATINIC EFFECT



confirmed in J.A.M.A.*

"administration of iron with food...reduce[s] the amount of iron available for hemopoiesis and limit[s] the effectiveness of treatment..."*

"the presentation of iron to the system as a chelate complex [iron choline citrate] permits its administration between meals..."*

CHĒL-IRON
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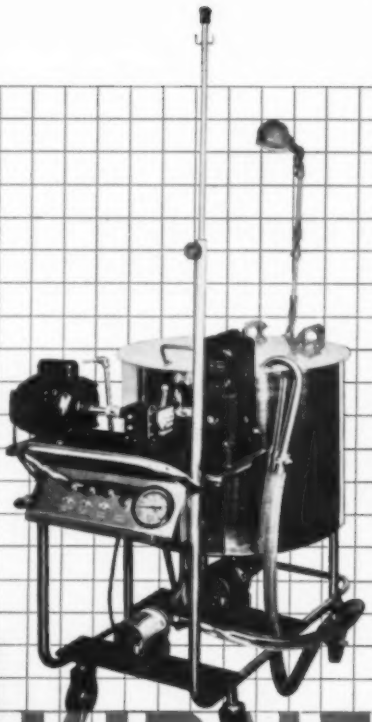

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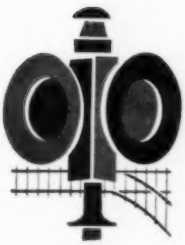

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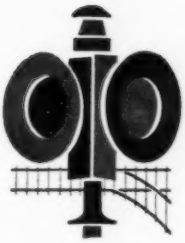

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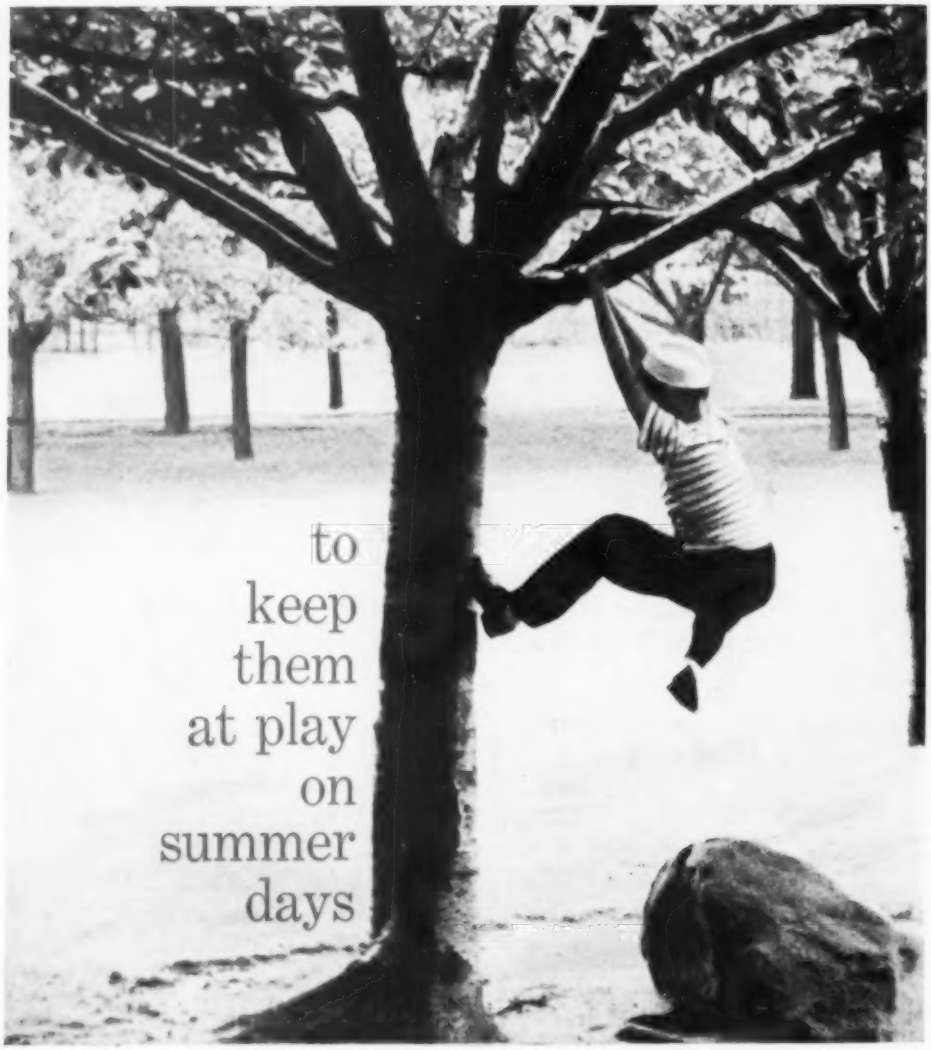

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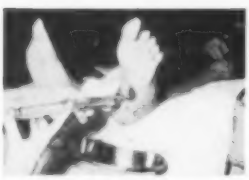

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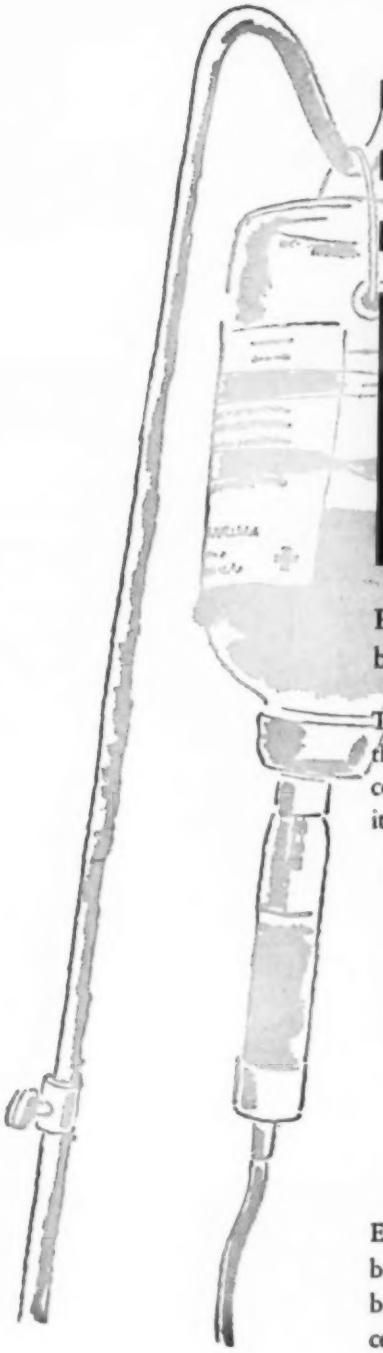

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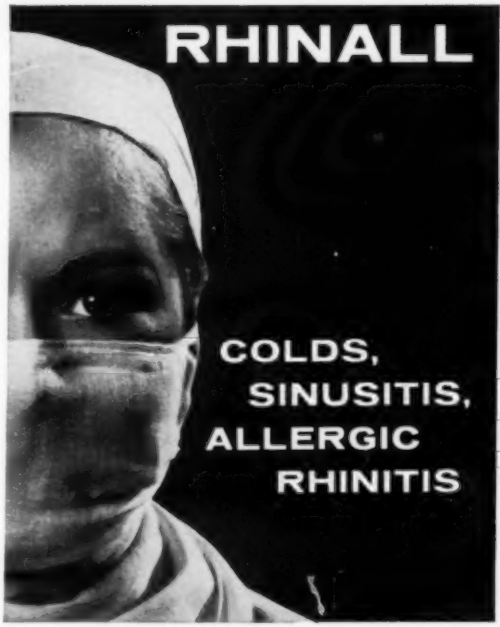

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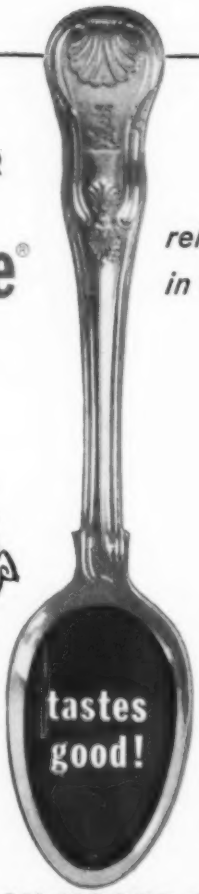

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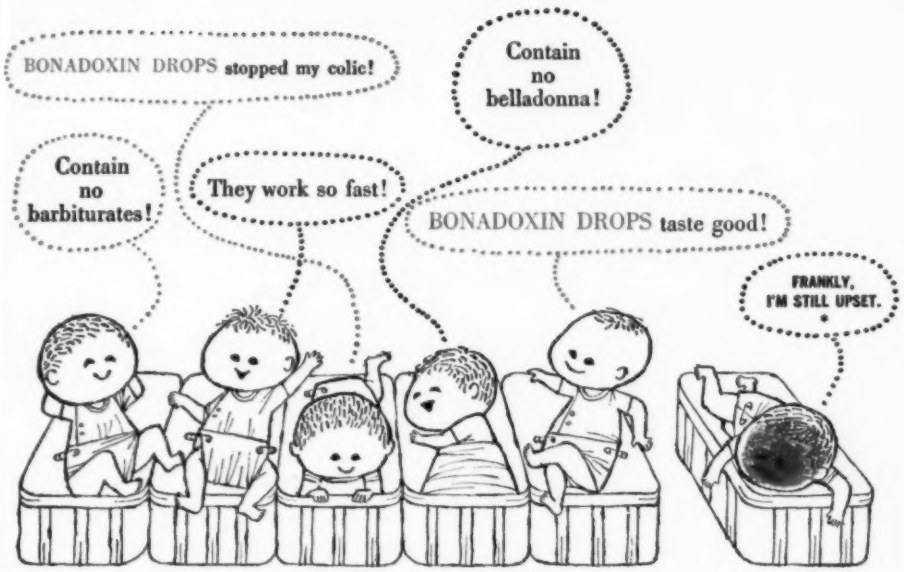

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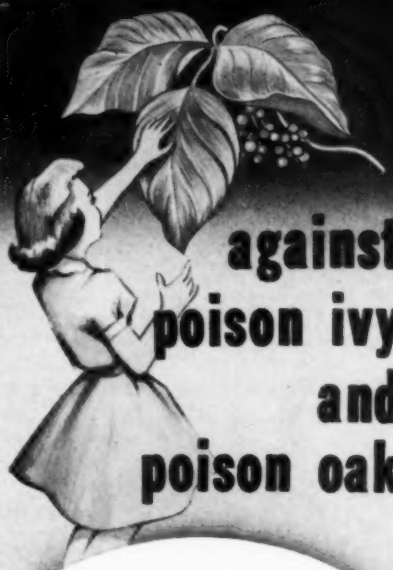

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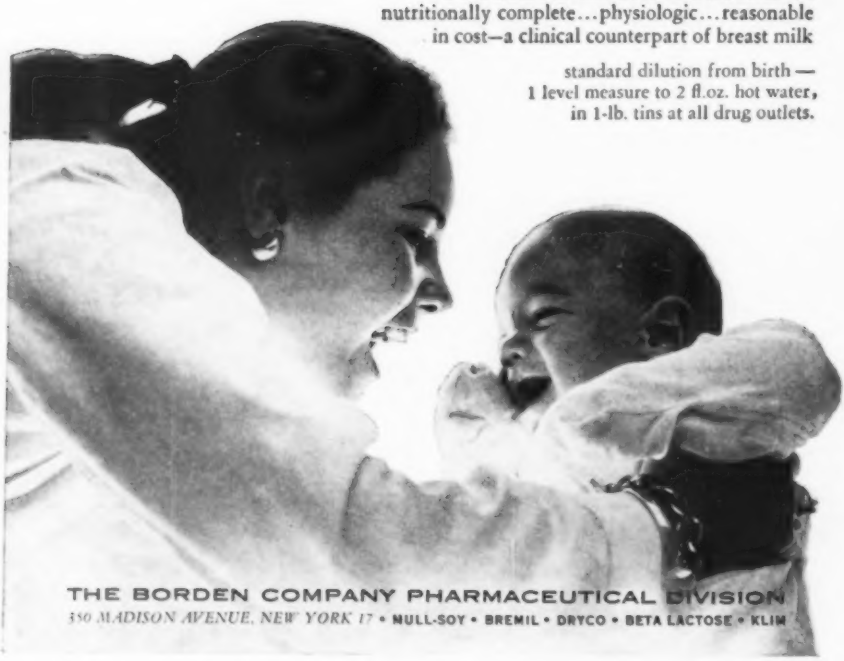

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